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The American Heart Journal

VOL. 15 APRIL, 1938 NO. 4

Original Communications

THE CAUSES OF DEATH IN PATIENTS WITH CONGESTIVE HEART FAILURE*

ROBERT H. WILLIAMS, M.D., AND JOHN RAINEY, M.D.
NASHVILLE, TENN.

MORTALITY statistics indicate that heart disease is the cause of death about twice as often as is any other condition. Cabot[1] analyzed 4,000 clinical and post-mortem records of patients dying at the Massachusetts General Hospital between 1896 and 1919 and found cardiovascular disease an important factor in 1,520 (38 per cent) of these individuals. This and other studies indicate that during the last few decades the number of deaths resulting from cardiovascular disorders has materially increased. For example, White[2] states that in Massachusetts the death rate from heart disease per 100,000 was 124 in 1915, 215 in 1925, and 341 in 1935. Such figures excite the query as to the cause of this striking increase. During the same period that the increase in morbidity and mortality has occurred, much time has been devoted to the study of heart disease and many valuable contributions have been made relative to the diagnosis and treatment of this condition. The factors usually mentioned to account for the apparent paradox are (1) the more frequent recognition of cardiac deaths in recent years; (2) increased life expectancy, which favors the more frequent development of degenerative heart disease; and (3) an increase in the "stress and strain" of life.

Assuming that a significant increase in morbidity and mortality from heart disease has occurred, the following questions are pertinent: (1) When heart disease is present in an individual, what factors, circulatory or noncirculatory, actually produce death? (2) What is the effect on these factors of the modern methods of treating congestive heart failure? (3) Is life prolonged by the use of these treatment methods? With these questions in mind the present study was undertaken.

METHOD OF STUDY

An analysis was made of the clinical and pathologic records of patients who gave a convincing history of congestive heart failure and

*From the Department of Medicine of the Vanderbilt University School of Medicine.

TABLE I

CAUSES OF DEATH IN PATIENTS WITH CONGESTIVE HEART FAILURE

TYPE OF HEART DISEASE	GROUP	NUMBER OF CASES	INCIDENCE %	AVERAGE AGE AT DEATH (YEARS)	AVERAGE DURATION OF LIFE‡ (YEARS)	EDEMA AT DEATH§ %	MYOCARDIAL EDEMA %	CHIEF CAUSES OF DEATH: UNCOMPLICATED CONGESTIVE HEART FAILURE % (DAYS IN HOSPITAL) 2−	2+	PULMONARY EMBOLISM AND INFARCTION %	PNEUMONIA %	UREMIA %	CEREBRAL VASCULAR ACCIDENTS %	SEPTICEMIA‖ %	CORONARY DISEASE %	MISCELLANEOUS %	SUPPLEMENTARY CAUSES OF DEATH: PNEUMONIA¶ %	PULMONARY EMBOLISM AND INFARCTION %
Hypertensive heart disease	A*	20	25	44	8	75	60	5	15	10	15	30	10	10	0	5	45	40
	B†	36	35	46	18	36	34	6	6	14	8	50	8	0	6	3	52	16
Arteriosclerotic heart disease	A	14	17	68	18	36	50	14	14	29	14	0	7	7	14	0	50	50
	B	14	13	65	40	29	21	7	0	7	44	7	0	0	21	14	64	21
Arteriosclerotic heart disease with hypertension	A	14	17	66	20	36	21	7	21	29	0	21	7	0	7	7	36	50
	B	12	12	61	24	17	17	0	8	17	8	25	0	8	17	17	50	33
Syphilitic aortic insufficiency	A	12	15	40	10	67	58	0	50	41	0	0	0	8	0	0	8	41
	B	12	12	38	11	17	33	8	17	17	17	0	0	0	17	25	25	33
Rheumatic heart disease	A	9	11	40	25	67	78	11	33	33	11	0	11	0	0	0	55	67
	B	18	17	33	32	23	44	11	11	11	17	0	22	17	0	11	67	28
Miscellaneous	A	12	15	44	12	33	25	16	16	0	25	8	8	8	8	8	8	25
	B	12	12	43	11	50	42	25	16	25	17	0	8	8	0	0	42	17
Total	A	81	100	51	11	53	48	9	23	22	11	12	7	6	5	5	35	44
	B	104	100	47	18	30	34	9	9	14	16	21	8	5	9	9	53	23

*Patients dying during 1926-1930.
†Patients dying during 1931-1935.
‡Median duration of life in months, after the onset of congestive symptoms.
§Patients with moderate or marked edema.
‖With or without endocarditis.
¶Total per cent, both as a primary and secondary cause of death.

who died and were subjected to post-mortem examination at the Vanderbilt University Hospital during 1926-1935. Only records of patients who had exhibited definite evidence of congestive failure at some time during the course of their disease and showed cardiac dilatation on post-mortem examination were included in this study. By limiting our material in this manner, we felt that in the group studied most of the factors which produced death would be related either directly or indirectly to cardiac disease.

In order to compare recent treatment results with those previously obtained in this clinic, the records of the patients dying of heart disease during 1931-1935 (Group B) were compared with those of 1926-1930 (Group A), (Table I and Fig. 1). The types of heart disease were classified as follows: hypertensive, arteriosclerotic (with or without hypertension), syphilitic aortic insufficiency, rheumatic, and miscellaneous. The latter group included a variety of conditions such as cor pulmonale, thyrotoxic heart disease, concretio cordis, congenital heart disease, gumma of the myocardium, myocardial infarcts following coronary embolism, etc. In some patients more than one form of cardiac disease existed, but usually one predominated, and this determined the classification.

In each case were noted the age of the patient at death, the duration of life after the first appearance of congestive failure, the amount of subcutaneous edema at death, and whether either the lungs or the liver showed congestion. Because of our interest in the mechanism of the beneficial action of diuretic drugs, the presence or absence of myocardial edema, as revealed by microscopic examination, was noted. An attempt was made in each case to determine the chief cause of death. This was found to be difficult in some instances. However, after considering the opinion expressed by the pathologist at the time of post-mortem examination concerning this point and after reviewing the clinical and pathologic records, we believe that this has been done with reasonable accuracy. It is true that in some subjects there were a number of conditions present, no one of which, had it operated singly, would probably have been sufficient to cause death. One usually was preeminent, however, and in our study this condition was designated the cause of death. Because of the frequency of pulmonary embolism and infarction and of pneumonia as supplementary causes of death, the total incidence of these was also recorded (Table I).

RESULTS

Incidence.—There were eighty-one cases during the years 1926-1930 and 104 during 1931-1935, which fulfilled the requirements mentioned above. In the latter series there was a relatively greater incidence of cases in the hypertensive and the rheumatic groups and a slight decrease in the other groups. The distribution of the various types of heart disease was found to correspond closely to figures given in other reports

from the South,[3, 4, 5] the vascular diseases constituting about 60 per cent and the rheumatic and syphilitic diseases, each about 15 per cent.

Age at Death.—The average age at death was between 35 and 45 years for all types of heart disease except the arteriosclerotic, in which it was about 65 years. It may be observed in Table I that these figures in general are lower for Group B than for Group A. This is due to earlier development of disease in many patients of the former group.

Duration of Life After Onset of Congestive Symptoms.—The median duration of life after the onset of congestive symptoms was found to be eleven months for Group A and eighteen months for Group B (Fig. 1). This increase in duration was present in the hypertensive, the arteriosclerotic and the rheumatic groups. On reviewing the ten-year "after histories" of 1,000 men suffering from heart disease, Grant[6] found that

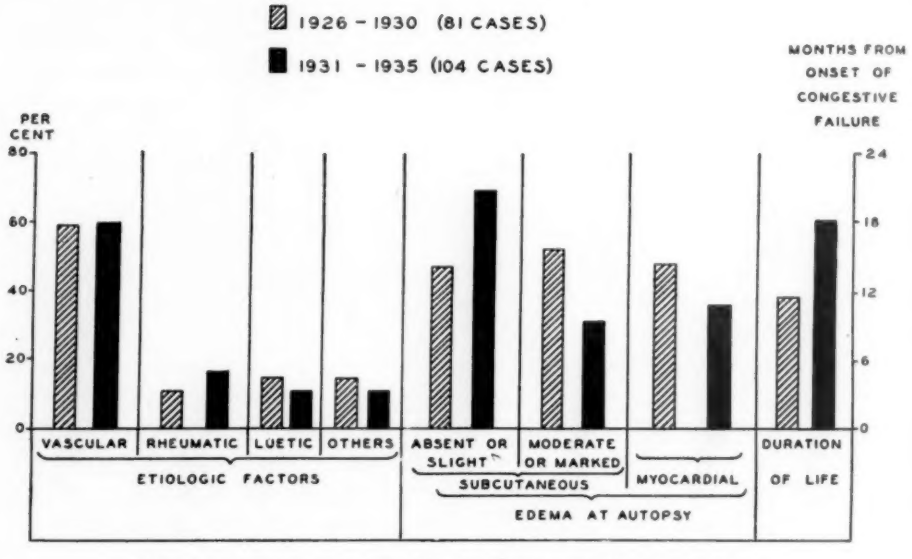

Fig. 1.—Congestive heart failure in cases coming to autopsy.

the duration of life, in the presence of venous congestion was two and one-half years. A large proportion of his patients had rheumatic heart disease. In Group B of our series the average duration in rheumatic subjects was thirty-two months, in the arteriosclerotic subjects forty months, and in the corresponding syphilitic group only eleven months. In manifest syphilitic aortitis Cabot found that, when "once the disease becomes known, it kills in most cases within two years from the first symptoms." On the basis of his study of hypertensive heart disease he concluded that "death usually follows within a year from the first serious evidence of stasis."

Congestion at Death.—Evidence of congestion of the liver and lungs was present in 75 per cent of the patients in Group A and 65 per cent in Group B. This decrease in congestion in Group B as compared with Group A was not as great as the decrease in the amount of edema pres-

ent at death in the members of Group B as compared with Group A. In the 1931-1935 group there was a definite reduction in the amount of subcutaneous edema at death in each type of heart disease, except in the miscellaneous cases, for 53 per cent in Group A exhibited moderate or marked edema as compared with 30 per cent in Group B. A corresponding difference was noted between Groups A and B in the incidence of myocardial edema (Fig. 1).

CAUSES OF DEATH

(Table I and Fig. 2)

The cause of death in most cases was due to congestive heart failure, pulmonary embolism or infarction (or both), pneumonia, uremia, cere-

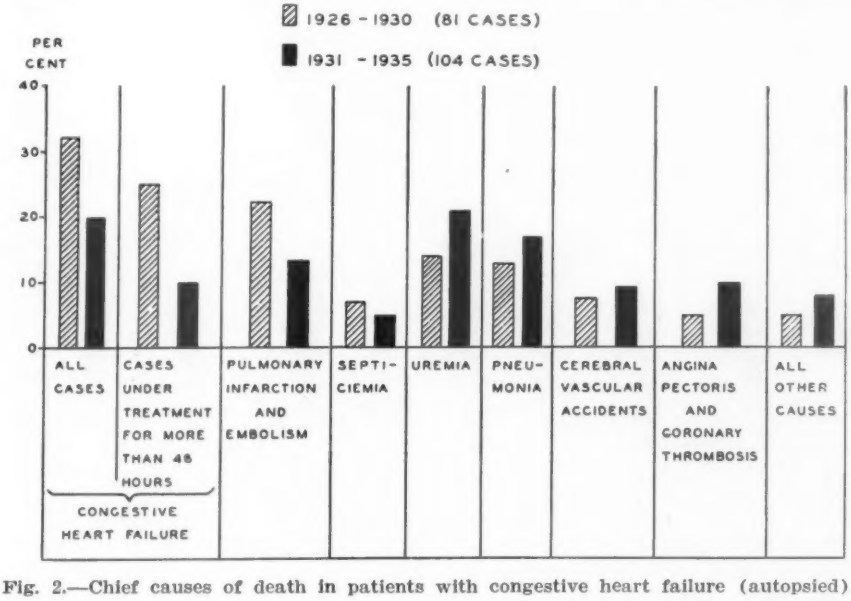

Fig. 2.—Chief causes of death in patients with congestive heart failure (autopsied).

bral vascular accidents, septicemia (with or without endocarditis), angina pectoris or coronary occlusion, and a few miscellaneous conditions. The rôle of each of these factors will be considered separately as follows:

1. *Congestive Heart Failure.*—According to reports in the literature, when once congestive failure has become manifest in patients with heart disease, death will result from congestive failure in from 30 to 40 per cent of the cases. Grant[6] found that 37 per cent of his patients with syphilitic aortic insufficiency died of congestive heart failure. Cabot[1] found that 34 per cent of his syphilitic patients and 33 per cent of his hypertensive patients died of this cause. Of 107 "pure mitral cases" he states "these cases seem to show that as a rule death does not occur in mitral disease by means of decompensation and passive congestion." Nevertheless, in 106 cases of mitral stenosis he found that forty-nine died of passive congestion.

We were interested in determining the frequency of congestive failure as a cause of death in patients with heart disease since the adoption of our present form of treatment. The incidence of this condition in the cardiac patients who died during 1931-1935 was compared with that of the 1926-1930 group. Whereas congestive failure accounted for 31 per cent of the deaths in the earlier group, it accounted for only 18 per cent in the 1931-1935 patients. We then divided the two groups according to whether the patients had been in the hospital for two days or less when death occurred, since time for response to treatment was usually insufficient if the patient had been hospitalized less than two days. Nine per cent of the patients in Group A, and the same percentage in Group B died of congestive heart failure within two days of admission to the hospital. Among those living longer than two days after their hospital admission, however, congestive failure accounted for 23 per cent of the deaths in Group A and for only 9 per cent in Group B. This pronounced decrease in the frequency of congestive heart failure as the cause of death in the 1931-35 group was observed in each etiological type of heart disease included in our study except the miscellaneous group. Here no decrease occurred. It is noteworthy that in syphilitic aortic insufficiency congestive failure accounted for 50 per cent of the deaths in 1926-1930, whereas it accounted for only 17 per cent in 1931-1935. In the arteriosclerotic type it accounted for 14 per cent in the first period and for none in the latter.

2. *Pulmonary Embolism and Infarction.*—A comparison of the occurrence of pulmonary embolism and infarction as the chief causes of death in the periods 1926-1930 and 1931-1935 reveals a marked reduction for the latter period. This decline is well-defined in the arteriosclerotic types (with and without hypertension) and in the rheumatic and syphilitic types, although there is a slight increase in the hypertensive group.

The incidence of these conditions as supplementary causes of death experienced a marked decrease in each type of heart disease in Group B, having occurred in 44 per cent of the cases during 1926-1930 and in only 23 per cent of the group during 1931-1935.

3. *Pneumonia.*—A definite increase in the incidence of pneumonia in heart disease was noted in Group B. This condition supervened in 35 per cent of Group A and 53 per cent of Group B patients. Sixty-four per cent of the patients with arteriosclerotic heart disease in the group during 1931-1935 developed pneumonia, and it was present in 67 per cent of the patients with syphilitic heart disease. As the chief cause of death pneumonia also showed a definite increase in the rheumatic, syphilitic, and arteriosclerotic groups.

4. *Uremia.*—As a cause of death in the patients with hypertensive heart disease uremia far surpassed all others, accounting for 50 per cent

of the deaths from 1931-1935. In the subjects without hypertension it caused only one death during this period.

5. *Cerebral Vascular Accidents.*—This was the lethal factor in 10 per cent of subjects with hypertensive heart disease in Group A and in 8 per cent in Group B. Cerebral hemorrhage was the condition usually encountered at necropsy. Cerebral accidents appeared with greater frequency in the rheumatic subjects than in the hypertensive ones, being the cause of death in 22 per cent of the former from 1931 to 1935. In these patients cerebral embolism was usually found at post-mortem examination. In a review of 330 cases in which death occurred as the direct result of cardiac disease, Willius[7] found embolic phenomena in 58 (17 per cent).

6. *Bacterial Endocarditis and Septicemia.*—These were the lethal factors in 6 per cent of patients of Group A and in 5 per cent of Group B. In the latter group 17 per cent of the deaths of patients with rheumatic heart disease were caused by these complications. Here they usually were manifestations of subacute bacterial endocarditis.

7. *Angina Pectoris and Coronary Occlusion.*—Each of the arteriosclerotic groups experienced a high incidence of angina pectoris and coronary occlusion. It is of interest that, whereas coronary disease caused no deaths from 1926 to 1930 in patients with syphilitic aortic insufficiency, it accounted for 17 per cent of deaths in this group from 1931 to 1935. Grant[6] found that it accounted for 9 per cent of the deaths in eighty-two patients who succumbed to this type of cardiac disease.

8. *Miscellaneous.*—Under this division have been placed a variety of conditions. One patient in the syphilitic group died of a ruptured aneurysm, and two died suddenly, possibly of ventricular fibrillation. Some of the other miscellaneous causes of death were mesenteric thrombosis, heart block, lung abscess, etc.

DISCUSSION

Although the number of cases is not large, the foregoing comparisons of the patients in Group B with those in Group A (Table I) seem to indicate that in recent years there has been a definite increase in the duration of life in patients who have suffered from congestive heart failure. This prolongation of life seems best accounted for by the more effective control of congestive failure. That this was obtained is indicated by the marked reduction in the number of patients during the period 1931-1935 who died primarily of congestive heart failure. This is further indicated by the distinct reduction in the 1931-1935 group of the amount of subcutaneous edema, myocardial edema, and hepatic and pulmonary congestion found at post-mortem examination. It also seems reasonable to attribute the noteworthy reduction in the incidence of pulmonary embolism and infarction in large measure to the better control

of passive congestion. The incidence of pneumonia, on the contrary, has shown a distinct increase. Pneumonia was present in 53 per cent of the subjects in Group B and was the second commonest cause of death in our series. We regard this as being due to the fact that with the better control of circulatory factors in cardiac disease life is prolonged, and, since patients with advanced heart disease are in poor general physical condition, the chances for the development of pneumonia are increased.

The reduction in the incidence of congestive heart failure as a cause of death is reflected not only in necropsy reports, but also by the increased number of patients discharged from the hospital as "improved." Since only about 20 per cent of the patients who entered the hospital with congestive heart failure died in the hospital and since only about 20 per cent of these patients who died were found at post-mortem examination to have congestive heart failure as the chief, immediate cause of death, it is evident that our mortality from congestive heart failure during 1931-1935 was approximately 4 per cent. Of those who were treated in the hospital for more than two days, this mortality was approximately 2 per cent.

If more effective control of passive congestion constitutes the explanation of the better therapeutic results obtained in the 1931-1935 group as compared with the 1926-1930 group, how was it brought about? The management of patients with heart disease as regards activity, diet, fluids, digitalis, and sedatives has remained essentially the same throughout the ten-year period. The only significant therapeutic change made during this period was the more intensive use of diuretics. This began in 1930. Since 1930 every effort has been made to keep patients "dry." All edematous subjects have been tested for tolerance to the various xanthine diuretic drugs, and edema has been treated by the use of the latter for two or three days each week, with or without salyrgan. The latter was employed freely in all cases except those exhibiting evidence of impaired renal function.

A survey of the group of patients who received frequent injections of salyrgan (Group B) reveals that only one, excluding patients with hypertension, died of uremia. Fifty per cent of the subjects in Group B who had hypertensive heart disease died of uremia. Most of these patients had either malignant or benign nephrosclerosis. It seems probable that the better control of edema in these patients protected a certain number from early cardiac death and allowed for progression of the degenerative changes in the kidney to take place. It is also possible that in subjects with occult renal injury the mercurial diuretics may have caused further damage to the kidneys. Wiseman,[8] however, records the administration of 270 injections of salyrgan to one patient in five years without apparent harm.

The data in Table I (Group B) reveal the cause of death in patients who had manifested congestive heart failure and had received the conventional treatment together with the intensive use of diuretics. In the subjects with hypertensive heart disease uremia stands first as a cause of death; in arteriosclerotic heart disease pneumonia is the outstanding lethal development, although angina pectoris and coronary thrombosis are common; in rheumatic fever embolism and pneumonia are the common terminating conditions, although congestive failure and bacterial endocarditis frequently occur.

The frequent occurrence of pulmonary infarction and pneumonia as supplementary causes of death in each type of heart disease should be emphasized. Impressed by the importance of these complications we have recently reduced the initial period of complete bed rest for our patients with congestive failure and have given careful attention to the problem of the prevention and treatment of respiratory infections.

SUMMARY AND CONCLUSIONS

A study has been made of the cause of death of patients who suffered from congestive heart failure and who had been subjected to post-mortem examination at the Vanderbilt University Hospital. Two groups, composed of patients who died during the years 1926-1930 and 1931-1935, were compared as regards underlying and immediate lethal factors.

Death from congestive heart failure and from pulmonary embolism and infarction distinctly decreased in frequency during the period 1931-1935. During this same period pneumonia, both as a primary and supplementary cause of death, increased in frequency, particularly in patients with arteriosclerotic heart disease.

Comparison of the two groups indicates that the duration of life after the onset of congestive symptoms has been distinctly prolonged in recent years. This is attributed to the better control of edema and has been brought about largely by the intensive use of mercurial and xanthine diuretics.

Intensive treatment with salyrgan did not increase the incidence of uremia in our group of nonhypertensive patients.

Uremia occurred with increased frequency in the 1931-1935 hypertensive group as compared with the 1926-1930 group. Whether the increased incidence of uremia in the subjects with hypertensive heart disease was due entirely to the prolongation of life which resulted from improvement in the treatment of heart disease (intensive use of diuretics), thus allowing progression of renal damage to occur, or whether in some instances the mercurial diuretics actually favored progression of renal disease cannot be stated with certainty.

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SOME PROBLEMS IN THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF ACUTE ARTERIAL OCCLUSION*†

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THE diagnosis of acute occlusion of the large arteries of the upper and lower extremities is seldom difficult. The symptoms and signs attending the abrupt closure of the main artery of a limb are usually of such character that the diagnosis may readily be made by one familiar with the condition. The differentiation of embolism and thrombosis as the cause of the sudden circulatory arrest is a more difficult problem since interruption of the blood flow, common to both embolism and thrombosis, plays such a dominant role in causation of the signs and symptoms present in the condition. It is our opinion, however, that a careful study of the signs and symptoms, particularly the sequence of their development, their location, and their severity, makes possible the differential diagnosis of embolism and thrombosis in the majority of cases. This report is mainly concerned with the symptom of pain in thrombosis and embolism, its possible causes, and its clinical significance. In addition, the prognosis and treatment of acute arterial occlusion are considered in the light of newer methods of therapy.

In a series of thirty-six cases of acute embolic occlusion pain was the initial symptom in twenty-three, or approximately 64 per cent. Pain of maximal severity at the onset was present in nineteen of these twenty-three cases, or approximately 53 per cent of the total. Although pain was the first complaint in the other four cases, it was described as a distress in the limb at the onset, and a definite interval of time elapsed before the pain reached its maximum severity. In six of the other seventeen cases the development of pain, numbness, and coldness appeared to coincide, and in the remaining eleven cases the sequence in the development of symptoms was numbness, or numbness and coldness, followed by pain. To sum up, then: pain was present as the initial complaint in 64 per cent of cases of acute embolic occlusion; it was of maximum severity at the onset in 53 per cent and was present in the later stages of the condition in 100 per cent of cases. It was noted that pain of maximal severity at the onset usually was located at the level of the occlusion, and much less often in the distal part of the affected limb, and that the pain present in the later stages of the condition was always

*From the Department of Medicine, University of Toronto, and the Medical Service, Toronto General Hospital.
†Read before the American Heart Association, Atlantic City, June 8, 1937.

located distal to the site of the occlusion. In view of the variation in the time of development, in the location, and in the severity of the pain present in different cases of acute embolic occlusion, it seemed to us unlikely that the origin of the pain could be identical in all instances.

It seems clear from the work of Lewis[1] that pain developing distal to the site of an arterial occlusion and in association with numbness and coldness is due to ischemia. This explains the cause of the late pain present in 100 per cent of our cases. On the other hand, ischemia does not appear to be an adequate explanation for the early pain occurring at the level of the embolic occlusion. When pain at the onset was referred to the level of the occlusion, we have found that it preceded the onset of numbness and coldness. It was always of short duration, often lasting for only a few minutes, and was succeeded by prolonged distress or actual pain in the distal part of the affected limb developing in association with, or followed by, numbness and coldness in the same area. With the shifting of an embolic clot from the aortic bifurcation to the femoral artery, the patient may give a history of an initial pain in the back, later in the lower abdomen and, finally, in the groin over the femoral artery. The short duration of the pain at the level of the occlusion and the change in the location of the pain, with a change in the position of the embolic clot, occurring in certain cases make ischemia from occlusion of collateral vessels at the site of the main obstruction, as proposed by Lewis,[1] an unlikely explanation for the cause of this early pain, in our opinion. It appears to us that spasm at the site of the embolus, as first suggested by Seifert,[2] is a more probable cause for the early localized pain in complete embolic occlusion.

Occasionally patients with an embolic occlusion of the femoral artery, or occlusion even at a higher level, will complain of an early pain of maximum severity in the popliteal space, in the upper part of the calf, or in the foot. In one of our cases an acute pain developed in the foot, which preceded the onset of numbness and coldness. As this pain appeared when the patient was walking about and was promptly relieved by alternate suction and pressure treatment, it seems apparent that ischemia was the cause of this early, severe, local pain occurring distal to the site of the occlusion. This conclusion is in agreement with that of Lewis as to the cause of local severe pain occurring distal to the site of the embolic occlusion.

In two of our cases the patients complained of severe, temporary pain localized to the popliteal space, which developed subsequent to an embolic occlusion at a higher level. In one of these cases an embolus was removed from the common iliac artery, and later, at autopsy, an embolus at the bifurcation of the popliteal artery was found. One of us (D. G.[3]) has suggested that the acute, localized pain in the popliteal space probably followed occlusion of the artery from a fragment of the proximal embolus, local spasm being the probable cause of the pain.

In this connection, it is interesting that Ross[4] has reported the relief of prolonged, acute pain in the popliteal space by excision of the occluded portion of the artery. The prolonged and localized character of the pain and its prompt disappearance following arteriectomy suggest local arteritis rather than ischemia as the causative factor for the pain in this instance.

In certain cases of embolic occlusion wherein a history of an acute early pain at the level of the occlusion is obtained, the pain, having remained localized to the site of the obstruction for a brief period, later spreads down the limb. When such a pain develops, it is of short duration and like the early localized pain precedes the development of numbness, coldness, and distress or pain arising in the extremity distal to the occlusion. At the present time no adequate explanation can be offered for the cause of this pain which spreads distally from the level of the occlusion.

The occurrence of an early as well as a late type of pain in many cases of acute arterial occlusion is of diagnostic importance. In our experience a history of an initial pain at the level of the occlusion is diagnostic of occlusion from embolism and never occurs in spontaneous thrombosis. The thrombotic attack, as a rule, begins with numbness and coldness, and the pain which follows these premonitory symptoms arises distal to the level of arterial closure. Like the late pain of embolism, it would appear to be of ischemic causation.

TREATMENT

The purpose of treatment of acute arterial occlusion is the early re-establishment of the blood supply of the affected limb. This may result from the development of an adequate collateral circulation or, in patients with occlusion from embolism, from removal of the obstruction by operation. Arteriotomy provides the only means whereby the obstruction may be removed and the continuity of the occluded artery restored. This is only possible in acute arterial occlusions due to emboli.

The satisfactory immediate results following early operation in a considerable percentage of cases of acute embolic occlusion made embolectomy the accepted method of treatment in this condition. Our experience with eleven cases treated by embolectomy has not been satisfactory. In the evaluation of this method of treatment it would appear that too much stress has been laid on the satisfactory results that may follow early operation and too little attention paid to the late results following embolectomy and to the percentage of spontaneous recovery of the circulation following acute arterial occlusion.

In connection with embolectomy we would like to point out that spontaneous recovery is not uncommon (Table I). In one case of complete occlusion of the aortic bifurcation spontaneous recovery occurred. Some months later this patient died of ventricular fibrillation, and at

TABLE I

IMMEDIATE RESULTS IN TREATED AND UNTREATED CASES OF EMBOLISM OF THE LARGE PERIPHERAL ARTERIES*

SITE OF EMBOLUS	FREQUENCY	PER CENT	RESULTS WITH TREATMENT				RESULTS WITHOUT SPECIAL TREATMENT†		OUTCOME UNCERTAIN AT DEATH‡
			CIRCULATION RESTORED		GANGRENE		CIRCULATION SPONTANEOUSLY RESTORED	GANGRENE	
			PAVAEX THERAPY	EMBOLECTOMY	PAVAEX THERAPY	EMBOLECTOMY			
Popliteal	16	24.6	3	0	2	0	3	6	2
Femoral	20	30.8	2	0	1	4	5	6	2
Iliac	6	9.2	0	1	3	1	0	0	1
Aortic bifurcation	9	13.9	2	2	0	1	1	2	1
Brachial	5	7.7	0	1	0	0	3	0	1
Axillary	6	9.2	0	2	0	0	3	0	1
Subclavian	3	4.6	0	0	0	0	1	0	2
Total	65	100.0	7 (10.8%)	6 (9.2%)	6 (9.2%)	6 (9.2%)	16 (24.6%)	14 (21.6%)	10 (15.4%)

*Embolic occlusion of the large arteries of the upper and lower limbs occurred 65 times in 41 cases. The analysis is based on the total number of extremities involved.

†No treatment aside from heat to the body.

‡Death as result of congestive heart failure or cerebral embolism occurred within twenty-four hours of the embolic attack. In three instances suction and pressure treatment was given.

autopsy complete obliteration of the aorta at the bifurcation was found. In a series of thirty-six cases of complete occlusion, of the common femoral artery in twenty and of the popliteal artery in sixteen, spontaneous recovery of the circulation occurred in approximately 20 per cent of each group. Among fourteen cases of complete occlusion of the arteries of the upper extremity, seven recovered without any special form of treatment; three recovered following embolectomy; and four died from the primary disease within a few hours of the onset of occlusion, before it was possible for recovery of the circulation to occur. When acute embolic occlusion of the arteries of the upper extremities occurs in patients not suffering from severe failure of the general circulation, spontaneous recovery would appear to be the rule rather than the exception, and one would question, therefore, the need for embolectomy or for any other special form of treatment in cases of embolism of the large arteries of the upper extremity.

Pearse[5] found that 52 per cent of 282 cases died within one month after operation, the chief cause of death being the primary disease and, to a lesser extent, recurrent emboli. In analyzing the operative results in 382 cases in Sweden, Nystrom[6] found that the late result was satisfactory in but 86, or 22.5 per cent of cases. Strömbeck,[7] who followed up 61 of these 86 patients, found one-third of this number living after five years and only three patients who were able to return to a gainful occupation.

These findings, which are in agreement with our own experience, go to show that the primary disease, and not the immediate restoration of the peripheral circulation, is the important factor in determining the late prognosis in acute arterial occlusion.

As the primary disease plays such an important rôle in both the causation and the prognosis of acute arterial occlusion from thrombosis and embolism, treatment directed toward the early restoration of the circulation by measures other than embolectomy would seem to be indicated. This has now been made possible through the introduction of alternate suction and pressure treatment by Herrmann and Reid[8] and Landis and Gibbon.[9] Alternate suction and pressure therapy has the advantage of being applicable to cases of thrombosis as well as of embolism, and in the treatment of the latter is not limited by the duration of the occlusion. We have treated ten consecutive cases of arterial embolism with alternate suction and pressure. The results have been extremely encouraging. In all cases the occlusion was of the main arteries of the lower extremities. In five of the ten cases the circulation of the affected limbs was restored. In four of the five successful cases, treatment was begun within five hours of the embolic attack. Two were cases of embolus of the aortic bifurcation; one was a case of embolus of the left common femoral and right popliteal arteries; in another the embolus was located in the common femoral artery; and in the fifth it was in the popliteal artery and was

associated with extensive secondary thrombosis. In two of the cases of bilateral occlusion, all pulses returned to both lower extremities within four months of the occlusive attack. In five cases this treatment was ineffectual. Two patients, both with occlusion of one popliteal and of the opposite femoral artery, were moribund when treatment was started, and at the time of death the outcome in respect to the limbs was uncertain. Another, with a popliteal embolus, had subacute bacterial endocarditis. The fourth patient had an embolus of the common iliac artery. And the last patient had bilateral emboli of the external iliac arteries. In three of the five failures, treatment was instituted twenty-four hours or more after the embolic attack, and in two during the first ten-hour period.

In four cases of spontaneous thrombosis, alternate suction and pressure failed to improve the circulation of the limb. Two of the four patients had thrombosis of the popliteal artery; one had thrombosis of the aortic bifurcation and of one common iliac artery; and the fourth had thrombosis of the superficial femoral artery. In two the involved extremities were gangrenous when treatment was started. All had advanced coronary disease and congestive failure. Amputation was necessary in three of the four cases, and death while in hospital was the outcome in every instance. The character of these cases was such as to constitute an unfair test for suction and pressure treatment. In the hands of others,[10, 11] it has produced encouraging results and it would appear to be a definite advance in the treatment of spontaneous thrombosis.

An embolus may initiate spasmodic contraction of the arterial wall in the region of the vessel when the clot is arrested. It is probable that this vasomotor reaction affects the anastomotic pathways as well as the main arterial channel. For this reason Denk[12] proposed the use of antispasmodic drugs and in six of ten cases of embolism achieved good results with intravenous eupaverine hydrochloride. Similarly favorable results were reported by de Takats[13] in two cases, and by Allen and MacLean[14] in one case. We have used papaverine hydrochloride in doses of ⅙ to ½ grain (0.166 gr. to 0.5 gr.) intravenously every four hours to supplement suction and pressure therapy in three cases of embolism. Because we wished to evaluate the latter form of treatment, the drug was withheld in all three until the recovery process was well advanced. We, therefore, have not data concerning the results of this other conservative form of treatment.

SUMMARY

In embolism of the large peripheral arteries, two distinct types of pain may arise. There may be pain at the level of the occlusion of short duration but of maximum severity at the onset of the attack. It merges into and is replaced by late pain of ischemic causation which arises in the distal part of the affected extremity. The late pain differs

greatly in character from the early distress, and it is felt that the early pain is probably due to arterial spasm initiated by the embolus. In thrombosis of the large arteries, similar early pain does not arise.

Attention has been called to the frequency of spontaneous recovery of the circulation in acute embolic occlusion of the larger arteries of the upper extremity.

The final result of treatment of embolic occlusion is largely determined by the severity of the associated primary disease. The results of suction and pressure therapy, in our experience, surpass those of embolectomy. We would agree with Herrmann and Reid and others that more conservative methods of therapy are indicated in the treatment of acute arterial occlusion. It is suggested that the ideal method of treatment for acute arterial occlusion is a combination of the nonoperative methods, namely: suction and pressure therapy, antispasmodic drugs, and heat to the body.

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THE ELECTROGRAM OF CARDIAC MUSCLE

II. The Lengths of the Stages of Activity*

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I

BY MEANS of the concepts developed in the previous paper,[1] it was possible to predict with considerable exactness the shape of electrograms obtained under various circumstances, but, in order not to complicate unduly that argument, the means of obtaining measurements of the duration of the excitation process from the recorded curves was not discussed. The measurements which are needed are: first, the time during which the muscle is in any stage of activity; second, the time during which the muscle is fully active and the length of the periods during which its activity is increasing and decreasing; third, the velocity with which the process spreads along the muscle. Information about two other matters is also desirable: first, a measure of the intensity of full activity (of two muscles both of which are fully active the manifestations of activity may be of much greater magnitude in one than in the other) and, second, the nature of the rate at which activity increases or decreases. This rate may be constant or a function of the stage of the process (activity may increase rapidly at first and more slowly later on or vice versa).

The last two items are complicated problems requiring a knowledge of the three first mentioned for their solution, and will not be dealt with in this communication. Of the first three, the first can be derived from the second, and methods for determining the third are well known. The concern of this paper will be, therefore, a description of the means of ascertaining the duration of the stages of increasing, full, and decreasing activity from a suitably recorded electrogram. Certain assumptions in the previous paper about the lengths of these processes will then be checked, and finally, since a somewhat different approach to the problem is necessary, the correctness of the method of analysis previously used can be tested. The experiment which is introduced serves the double purpose of illustrating the application of the concepts theoretically derived and of testing their validity.

II

Muscle does not become active instantaneously. The active process spreads with a given velocity so that one length of muscle will be be-

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coming active, another will be fully active, and a third will be regressing from the active state. The lengths which are in transition are the distances over which the potential difference which exists between resting and active muscle must be distributed. It is possible to represent the potential difference either by a chain of doublets distributed along the transitional region or by a single positive and a single negative pole located at its beginning and end, respectively. Conversely the length of the doublet chain or the distance apart of the positive and negative poles measures the length of the transitional region. *A B C D* (Fig. 1A) represents an excitation process which travels over a muscle fiber from left to right, *A B*, *B C*, and *C D* constituting the stages of increasing, full, and decreasing activity, respectively. *E* is an electrode. It has been shown[1] that the transitional process gives rise to a train of doublets and that such a train is equivalent to a single positive and a single negative

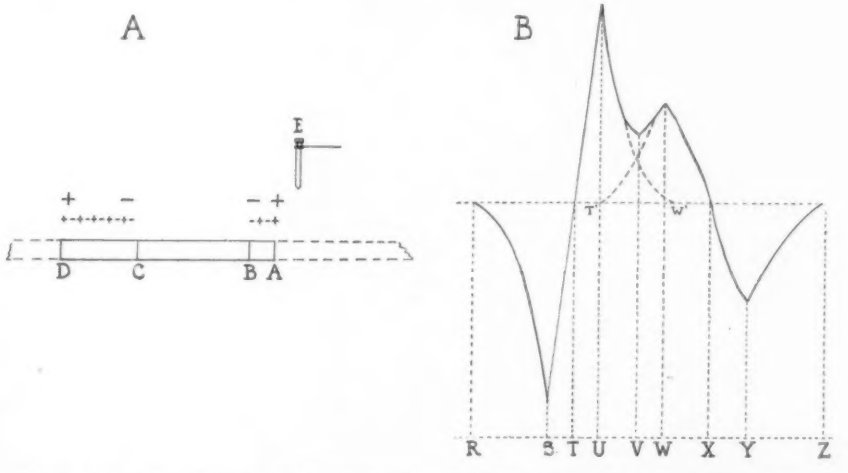

Fig. 1.—A. An electrode *E* is represented in close proximity to a strip of muscle along which the excitation process *A B C D* is passing from left to right. From *A* to *B* the muscle is increasing in activity, from *B* to *C* it is fully active, and from *C* to *D* the muscle is decreasing in activity. The potential differences between active and resting muscle which must be distributed over the transitional regions are represented both as chains of doublets (pairs of positive and negative poles infinitely close together) and as dipoles (single positive and single negative pole separated by a finite distance).

B. An hypothetical electrogram is shown such as would be produced by the passage of the potential differences depicted in *A* under the electrode. *R S T U W'* is the accession deflection; *T' W X Y Z* is the regression deflection.

S and *U* indicate the arrival of *A* and *B*, respectively, beneath the electrode and *W* and *Y* the arrival of *C* and *D* respectively.

From *T'* to *W'* the electrogram is produced by electrical effects resulting from both the accession and regression of activity.

pole separated by its length. If this latter concept is used the accession* deflection of the electrogram is written by the positive and negative poles located at *A* and *B*, respectively, as they pass under the electrode. The maximum positive effect may be expected to occur, therefore, when the

*It was shown in the previous paper that the electrogram is the sum of two diphasic curves. The first and more rapid, the result of electrical changes accompanying the accession of activity, is called the accession deflection; the second and slower, caused by electrical changes which accompany the regression of activity, is called the regression deflection.

positive pole is immediately beneath the electrode *E*, and the maximum negative effect when the negative pole is in this position. *S U* (Fig. 1B) measures accordingly the duration of the stage of increasing activity and *W Y* the stage of decreasing activity. Since *U* signals, furthermore, the end of the stage of increasing activity and *W* the beginning of decreasing activity, the interval *U W* measures the duration of full activity.

In this simple analysis no account has been taken of the fact that as the forward member of the dipole approaches the electrode, the effect of the hinder one is also increasing. While the effect of the forward member is maximum when it is directly beneath the electrode, this effect is counterbalanced to a certain extent by the proximity of the hinder member. It is consequently not perfectly clear that the resultant effect will be maximum when the forward member is beneath the electrode, particularly if the two members are close together. Wilson, Macleod, and Barker[2] have, in fact, shown that when the two members of a dipole are close together the maximum and minimum points of the curve do not occur exactly at the time when the corresponding members of the dipole are directly beneath the electrode. It is necessary, therefore, to learn whether the intervals between the maximum and minimum points of the curve measure the stages of activity with a reasonable degree of accuracy. The most satisfactory way to solve this problem is to derive a mathematical expression for the potential of the electrode at any moment and to ascertain analytically its maxima and minima. For this purpose it is convenient to deal with trains of doublets. Since both accession and regression deflections are produced by trains of doublets which differ only as to length and polarity, it is necessary to consider only three phases of the problem: (a) when the doublet train is shorter than the muscle, (b) when it is longer, and (c) when it is of equal length.

A muscle fiber, an electrode (*E*), and a short train of doublets (Fig. 2A) illustrate the conditions existing when the doublet train is shorter than the muscle. The long axis of the muscle fiber coincides with the x axis in a system of rectangular coordinates (Fig. 2B). The tip of the electrode is at a distance b from the origin on the y axis. x represents the position of the head of the train of doublets supposed to be travelling over the muscle from left to right, and L is the length of the doublet train. For the sake of simplicity the velocity V with which the doublet train travels is assumed to be unity, so that a unit of time and a unit of distance are represented by equal intervals on the graph. If then, the effect of any doublet upon the electrode is given by the formula

$$P = \frac{\mu \operatorname{Cos} \theta}{R^2},$$ the effect of the whole train will be

$$1.\quad P = \mu \int_{x-L}^{x} \frac{-x'}{(x'^2 + b^2)^{3/2}} = \frac{\mu}{\sqrt{x^2 + b^2}} - \frac{\mu}{\sqrt{(x - L)^2 + b^2}}.$$

This expression defines the effect upon the electrode for any position of the doublet train so long as all of it is on the muscle fiber. A graph of this function is also shown in Fig. 2B. To ascertain the maximum and minimum values of this function, it is necessary only to differentiate it with respect to x and equate the derivative to zero. This gives the equation

$$2.\quad D_x P = \frac{\mu (x - L)}{[(x - L)^2 + b^2]^{3/2}} - \frac{\mu x}{(x^2 + b^2)^{3/2}} = 0.$$

Obviously neither $x = 0$ nor $x = L$ is a root of this equation.

Consequently the maximum and minimum values of the function do not accurately signal the arrival of the head and tail of the doublet train,

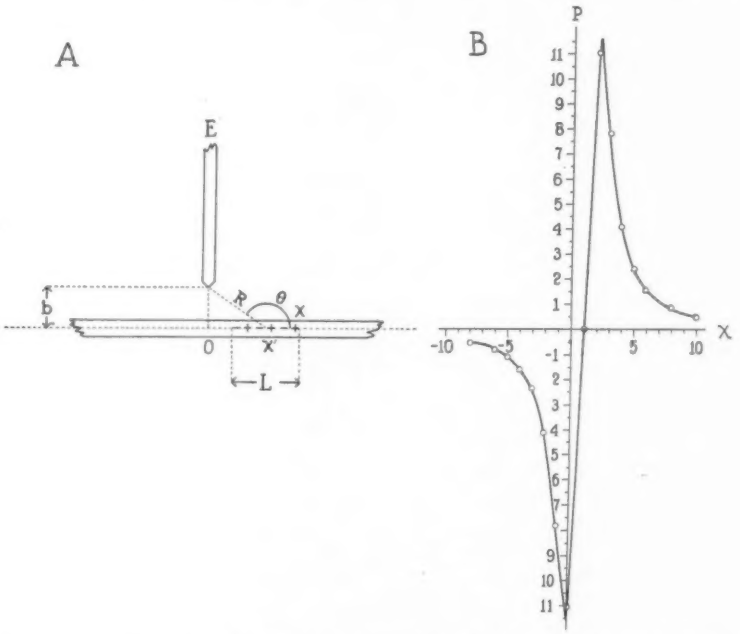

Fig. 2.—A. A short train of doublets travelling along a muscle strip is shown in relation to the exploring electrode E. L is the length of the doublet train; b the distance of the tip of the electrode from the muscle; X the distance of the head of the doublet train from the origin 0; X' the distance of any doublet in the train from the origin; R the distance of the doublet at X' from the tip of the electrode; Θ the angle between R and the line along which the doublets are travelling.

B. The graph of the function is plotted in which

$$P = \frac{\mu}{\sqrt{X^2 + b^2}} - \frac{\mu}{\sqrt{(X-L)^2 + b^2}}$$

i.e., the graph of the potential change produced in E by the passage of the doublet train along the muscle strip.

respectively, beneath the electrode, and the statement first made, that $S\ U$ (Fig. 1) measures the duration of the phase of increasing activity, is not strictly correct.

During the regression of activity the signs of the doublets are reversed and the train is represented as longer than the muscle over which it travels (Fig. 3). It is simplest to consider the problem in three parts:

first, the period during which the head of the doublet train is in the act of progressing over the muscle; second, the period during which the muscle is completely covered by the doublet train; and third, the period during which the tail is passing over the fiber. Fig. 3A represents the first of these situations. The symbols have the same notations as before. *A* and *B* are the abscissae of the ends of the muscle strip.

In this case the potential of the electrode is defined by the equation

$$3.\quad P = \mu \int_{A}^{x} \frac{x'}{(x'^2 + b^2)^{3/2}} = \frac{\mu}{\sqrt{A^2 + b^2}} - \frac{\mu}{\sqrt{x^2 + b^2}}.$$

This expression defines the potential of the electrode for the interval $X = A$ to $X = B$ or from the time of the first beginning of activity till the head of the active process reaches B. During this period the curve will reach its maximum value when $X = 0$, for $D_x P$ equated to zero gives the equation

$$4.\quad D_x P = \frac{-\mu x}{(x^2 + b^2)^{3/2}} = 0.$$

Obviously 0 is a root of this equation.

During the second stage (Fig. 3B) the potential of the electrode remains constant at the value it attained when the doublet train reached *B* since, for every doublet that passes off at *B*, one comes on to the strip at *A*. A constant relationship is therefore maintained between the doublets to either side of the electrode. Whether the potential of the electrode is zero, negative or positive, depends on whether the absolute value of *A* is equal to, greater than, or less than, that of *B*. The potential of the electrode is given by the equation

$$5.\quad P = \frac{\mu}{\sqrt{A^2 + b^2}} - \frac{\mu}{\sqrt{B^2 + b^2}}.$$

This expression defines the potential of the electrode for $[L - (B - A)]$ V seconds.

During the final period x represents the position of the tail of the doublet train (Fig. 3C). The potential of the electrode is expressed by the equation

$$6.\quad P = \int_{x}^{B} \frac{x'}{(x'^2 + b^2)^{3/2}} = \frac{\mu}{\sqrt{x^2 + b^2}} - \frac{\mu}{\sqrt{B^2 + b^2}}.$$

The duration of this stage is of course equal to that of the first. The curve will reach its minimum value, furthermore, when $X = 0$ for $D_x P$ equated to zero gives

$$7.\quad D_x = \frac{\mu x}{(x^2 + b^2)^{3/2}} = 0,$$

and zero is a root of this equation.

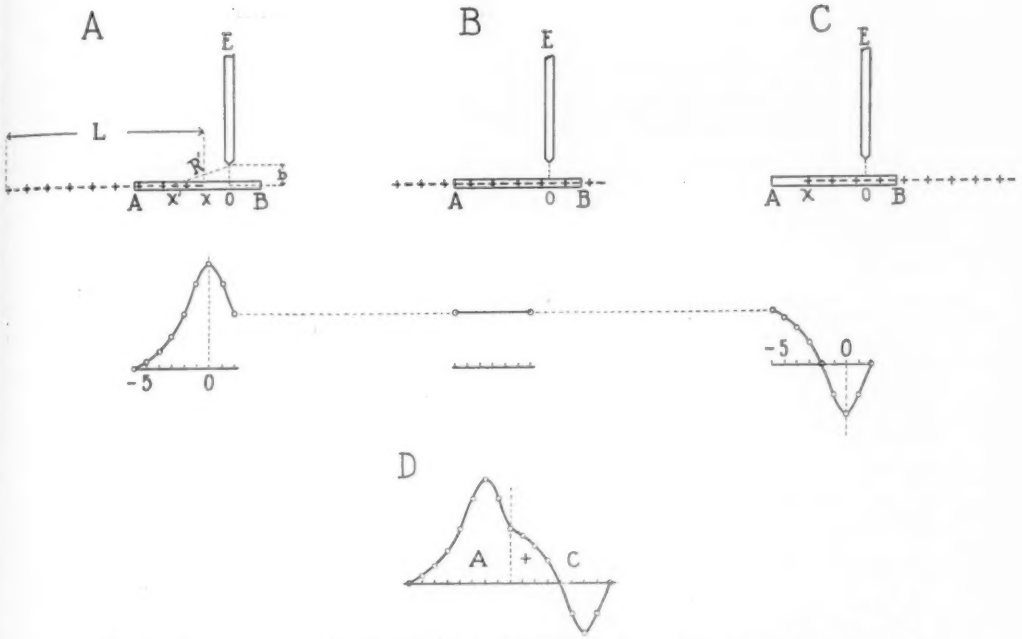

Fig. 3.—A. A short strip of muscle is represented over which a train of doublets longer than itself is travelling from left to right in relation to an exploring electrode E. b is the distance of the tip of the electrode from the muscle; AO the distance of the left end of the muscle from the origin 0; OB the distance of the right end from 0; XO the distance of the head of the doublet train from 0; $X'O$ the distance of any doublet that is on the muscle from 0; R the distance of the doublet at X' from the tip of the electrode. Beneath the diagram of the muscle strip and the electrode is a graph of the function:

$$P = \mu \left[\frac{1}{\sqrt{A^2 + b^2}} - \frac{1}{\sqrt{X^2 + b^2}} \right]$$

i.e., a graph of the potential change produced in E by the passage of the doublet train onto the muscle.

B. The muscle strip is represented during the period when it is completely covered by the doublet train. The potential of E remains constant during this period because for every doublet that passes onto the fiber at A, one passes off at B. The potential of E during this period is

$$P = \mu \left[\frac{1}{\sqrt{A^2 + b^2}} - \frac{1}{\sqrt{B^2 + b^2}} \right]$$

Below is a graph of the potential of E during this period connected by a dotted line with the graph of the preceding period.

C. The muscle strip during the period that the doublet train is passing off the fiber. X now indicates the position of the *tail* of the doublet train. Below is the graph of the function

$$P = \mu \left[\frac{1}{\sqrt{X^2 + b^2}} - \frac{1}{\sqrt{B^2 + b^2}} \right]$$

i.e., the graph of the change of the potential of E caused by the passage of the doublet train off the fiber. The preceding graphs are connected with it by a dotted line. By connecting these three segments together the complete graph of the electrical effect of the passage of the doublet train over the fiber is obtained.

D. The graph of the effect upon the electrode of the passage of a train of doublets equal in length to the fiber; sections A and C are connected but B is omitted.

Therefore, when the doublet train is longer than the muscle over which it travels, the maximum and the minimum peaks of the electrogram accurately signal the arrival of its head and tail, respectively, beneath the electrode. This is also true when the length of the train is equal to that of the muscle, for under these circumstances the second part of the analysis is simply omitted (Fig. 3D). In other words the central flat portion of the curve disappears.

Although derived in a different way, equation 1 is of the same form as the equation which Wilson, Macleod and Barker[2] obtained in their discussion of linear excitation, so that it is permissible to make use of their reasoning in regard to the maxima and the minima of the function. They showed that in general the interval between the maximum and the minimum peaks of the curve is greater than that which separates the positive and negative elements of the dipole, and the greater the distance between the tip of the electrode and the muscle (b) the greater is the disparity. Their reasoning was based upon the fact that when the two elements of the dipole are very close together (when it approximates a doublet*) the interval between the maximum and minimum peaks is dependent upon b (distance from electrode tip to muscle) alone. When this fact is taken in conjunction with the demonstration which has just been made, that when the length of the train of doublets or the distance which separates the elements of the dipole is equal to or greater than the length of the muscle it is accurately measured by the interval between the maximum and the minimum peaks of the electrogram regardless of the value of b, it is logical to conclude that the greater the interval (if this is less than the length of the muscle) between the elements of the dipole, the more accurately this interval is measured by that between the maximum and minimum peaks of the electrogram. When b is small and L is by comparison large, no appreciable error is introduced, therefore, by using the interval between the peaks of the electrogram as a measure of the length of a transitional stage, even if this stage is shorter than the muscle. What error there is will be greater in the case of the stage of increasing activity, but even in this case it will not be great for as will be shown subsequently, the length of this stage is several millimeters, whereas the distance of the electrode from the muscle is probably less than 0.1 mm.

If the graph of equation 1 is compared with the first part of the theoretical electrogram (Fig. 9 or 10 of the foregoing paper), it will be seen that the two are of identical shape. If the graphs of equations 3, 5, and 6 are connected seriatim, they also will be found to be identical with the graph of the effects of the regression of activity (Fig. 11 of the previous article). Without further demonstration it may be stated,

*For convenience the term dipole is used to designate a positive and negative pole separated by a finite distance in contradistinction to a doublet, the positive and negative poles of which are infinitely close together. A dipole is equivalent to a chain of doublets.

therefore, that any of the theoretical electrograms illustrated in the previous paper may be reproduced by combining the graphs of appropriate mathematical expressions. As it happened, the shapes of the theoretical electrograms were arrived at first by means of this sort of mathematical analysis. The graphic method was devised later because under certain circumstances the mathematical procedure becomes very cumbersome. Under the simple circumstances that have been dealt with so far, the mathematical analysis can be used as satisfactorily as the graphic one. But if the problem is complicated, as for instance, if the duration of a stage of activity were different at one end of a muscle from that at the other, the mathematical analysis would become too complex to be useful. In the graphic method it would then be necessary only to make the corresponding rectangles of different dimensions. It is possible also that the graphic method gives a clearer insight into the mechanisms whereby the electrogram is produced. Because of its greater flexibility and clarity the graphic method is in general to be preferred, but it is difficult by means of it to demonstrate the significance of the maximum and minimum points of the curve. For this reason and because the mathematical analysis is an excellent check on the validity of the graphic method, it has been briefly discussed.

III

To illustrate the application of the concepts which have been developed and to test their validity, an experiment was performed. The apparatus and arrangements were similar to those employed in the previous investigations except that two simultaneous records were taken, one from the central region of the auricle and one from a point near the auriculoventricular junction. It was possible in this way to learn the form of the curves from these two points and further to ascertain the velocity of transmission of the impulse. In Fig. 4A is such a pair of curves. They resemble in form the curves taken from similar positions in the previous paper (Fig. 10C and 11C). Without moving the electrodes, another record was taken after warming the heart by flushing it with warm saline solution (Fig. 4B). The accession deflections before and after warming are similar. The upward peak of the curve from the central portion of the auricle after warming (Fig. 4B, a_2) is slightly lower than the corresponding peak of the curve at room temperature (Fig. 4A, a_2) but the general form of the two is the same. This distortion probably results from the fact that the auricle was not warmed symmetrically. The regression deflections are, however, markedly different. In the set taken at room temperature, they have the forms that are expected (previous paper Figs. 10 and 11). In the curve from the central portion of the auricle the first upward phase (r_1) is concealed within the accession deflection, the flat portion coincides approximately with the isoelectric line and is followed by the final downward deflection (r_2). In

the curve from the vicinity of the auriculoventricular junction, the first upward deflection (r_1) is again concealed in the accession deflection, the flat portion is above the isoelectric line and is followed by a downward deflection (r_2), which is smaller than that of the curve from the center. After warming, the regression deflection of the curve from the central region becomes definitely diphasic with no flat central portion, and the two phases are approximately equal. The curve from the auriculoventricular junction also becomes diphasic, but the upward phase (r_1) is much larger than the downward (r_2). After warming, both summits of the regression deflection (r_1 and r_2) are visible, and the distance be-

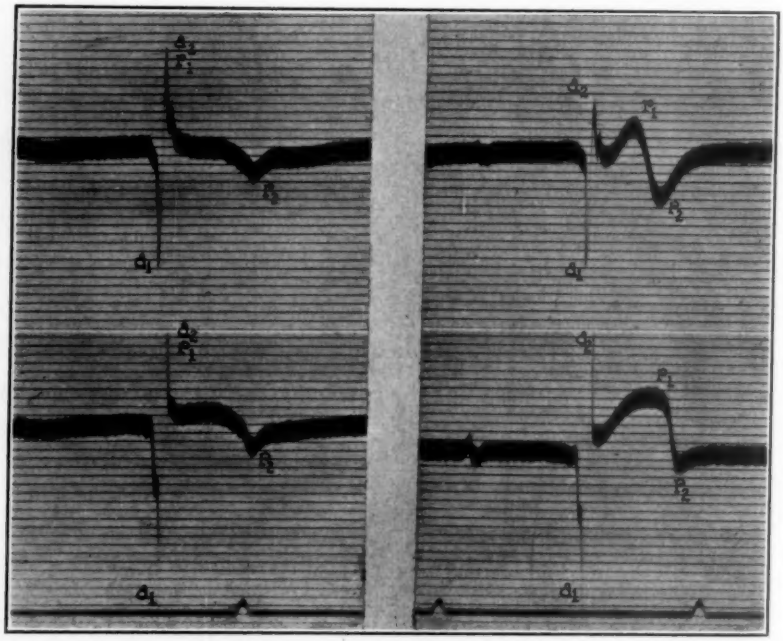

Fig. 4.—A. A pair of electrograms is shown taken from the anterior surface of a frog's auricle at room temperature. The upper curve was derived from the central region of the auricle and the lower one from a point 5 mm. nearer the auriculoventricular junction. a_1 and a_2 are the downward and upward peaks of the accession deflection; r_1 and r_2 are the upward and downward peaks of the regression deflection. r_1 is concealed in a_1 a_2. The flat portion of the upper curve which connects r_1 and r_2 coincides approximately with the isoelectric line. The corresponding part of the lower curve is above the isoelectric line.

B. A pair of electrograms is shown taken from the same points as in A after the preparation was warmed. r_1 is now visible in both curves, and the flat portion has disappeared. The time marked indicates seconds.

tween them, and therefore the duration of the phase of decreasing activity, can be easily measured. In the case of the curves taken at room temperature, the measurement of the duration of the regression process is necessarily inaccurate, but a very good approximation to it can be made by assuming that the summit of the upward peak is at the center of the accession deflection. These measurements are given in Table I.

Since the time at which the rapid upstroke of the accession deflection crosses the isoelectric line corresponds to the time at which the center of

the stage of increasing activity is beneath the electrode, the interval between the crossing of the isoelectric line in the top curve and the crossing in the bottom curve represents the time necessary for the impulse to travel from one electrode to the other. From this measurement and the distance between the electrodes the velocity with which the process of activation travels can be obtained. This velocity increases with increase in temperature.

In practice the accurate measurement of the velocity is attended with considerable difficulty. The velocities given in Table I are corrected as far as possible. But since the error in measuring the distance between the electrodes is approximately 10 per cent, they are inaccurate to this extent. Great accuracy is not essential, however, for the purposes of the present argument.

TABLE I

	VELOCITY OF IMPULSE (MM./SEC.)	DURATION OF ACCESSION PROCESS (SEC.)	DURATION OF REGRESSION PROCESS (SEC.)	DURATION OF FULL ACTIVITY (SEC.)	LENGTH OF ACCESSION PROCESS (MM.)	LENGTH OF REGRESSION PROCESS (MM.)	LENGTH OF PHASE OF FULL ACTIVITY (MM.)
Room temperature	166	0.015	0.33		2.5	55	
After warming	218	0.015	0.11	0.17 to 0.20	3.3	24	37 to 44

One further measurement should be recorded, namely, the length of the auricular muscle from the sinus venosus to the auriculoventricular junction. Making this measurement is difficult when the heart is in place because its surface is curved and part of it is inaccessible or accessible with difficulty. Only a rough estimate can, therefore, be made. It was from 20 to 25 mm.

IV

The most striking fact in Table I is the very marked disproportion between the lengths of the accession and regression deflections in the curves taken at room temperature. The regression process is more than twenty times as long as the accession process. The duration of full activity cannot be ascertained because the preliminary upward deflection (r_1) of the regression process is concealed within the accession deflection, but its duration must be very brief. It will, therefore, be seen that the conditions assumed formerly[1] to be present are justified. The concept then proposed was that the excitation process consists (1) of a brief stage during which activity is increasing, (2) of a very brief period of full activity, and finally (3) of a long stage of decreasing activity. The assumption that the regression process is usually longer than the muscle over which it travels is also confirmed. The distance travelled by the impulse in this experiment was 20 to 25 mm. (distance from sinus

venosus to ventricle along the anterior surface of auricle) whereas the length of the regression process was 55 mm.

An essential point in the conception of the regression deflection as developed in the present study and in the preceding is that it is a diphasic process. It has, however, been necessary to assume that the first of the regression phases is usually concealed within the larger accession deflection. That this is a possible state of affairs is obvious, but it may be well to summarize the evidence for its probability. In the first place, a theory which requires the existence of an upward phase for the regression process satisfactorily explains the displacement of the flat portion of the electrogram above and below the isoelectric line as well as the shape and size of the terminal deflection. Second, under certain circumstances, such as the application of heat, the regression deflection becomes obviously diphasic (Fig. 4B and in the previous paper, Fig. 9).

The use of heat to bring out the diphasic character of the regression deflection resulted from reasoning in the following manner. Since under ordinary circumstances the upward phase of the regression deflection is small as compared with the accession deflection, it seemed probable that if its amplitude could be increased in some way, evidence of its existence might be obtained. It was observed that increase in temperature decreases the duration of the regression process, and for theoretical reasons* it was believed that a decrease in duration should be accompanied by an increase in magnitude. The curves in Fig. 4B fulfill this prediction. The upward phase is now easily seen in the curves from both portions.

The measurements in Table I indicate that after warming the heart the length of the regression process is equal to that of the course over which it travels. Under these circumstances the flat central portion should disappear (Fig. 3D), and this deduction too is borne out by the experimental curves. That the stage of full activity would be increased could not have been predicted, for no method of analysis capable of bringing out this fact was hitherto available. What its significance may be will require further investigation. This ability to predict with some accuracy the behavior of the electrogram under varied circumstances would seem to be added evidence for the validity of the concepts developed.

SUMMARY

1. A method for measuring the stages of increasing, full, and decreasing activity of cardiac muscle from suitably recorded electrograms is described and the critique of the method discussed.

*It has been shown that the electrical activity of a minute segment of muscle can be represented by a rectangle whose height is proportional to its magnitude and whose length is proportional to its duration. If it is assumed that the difference of potential between active and resting muscle is always the same, it must follow that the area of the rectangle which represents the electrical effect must remain constant. While any reduction in the length of the regression process will decrease the duration of the effect (length of the rectangle), this must be accompanied by a proportional increase in the magnitude of the effect (height of the rectangle) because the total potential difference between active and resting muscle is now distributed over a shorter stretch of muscle, and each muscle segment will contain a proportionally greater portion of it.

2. A mathematical analysis of the electrogram has been used to check a previously described graphic one.

3. Further evidence has been brought forth for the concept that the electrogram of cardiac muscle consists of two diphasic curves (an accession and a regression deflection) produced by potential differences distributed over that portion of the muscle which is undergoing transition from resting to active state and vice versa.

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THE VENTRICULAR DEFLECTIONS IN MYOCARDIAL INFARCTION

An Electrocardiographic Study Using Esophageal and Precordial Leads*

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THE attempts to determine the sites of myocardial infarcts by the recognition of characteristic electrocardiographic curves started in 1928 when Parkinson and Bedford[1] demonstrated that there were two general types of curves obtained from patients who had suffered from coronary thrombosis. They called these the T_1 and the T_3 types. In the T_1 type there was upward displacement of the RS-T segment and inversion of T-wave in Lead I, while in Lead III the RS-T segment was displaced downward and the T-wave was sharply upright. In the T_3 type the RS-T segment was displaced upward in Lead III and downward in Lead I and the T-wave was inverted in Lead III and upright in Lead I. In the following year Barnes and Whitten[2] showed that the T_1 type was frequently associated with infarction of the anterior surface and apex of the left ventricle, i.e., in the distribution of the anterior descending branch of the left coronary artery, and the T_3 type with infarction of the posterior and basal part of the left ventricle, i.e., in the distribution of the posterior circumflex branches of both right and left coronary arteries. Gilchrist and Ritchie,[3] however, among others, considered that localization by means of RS-T and T-wave changes was not infallible when they failed to obtain good correlation between the site of the infarct and the electrocardiographic pattern. Later Wilson and his associates[4] found that a large Q-wave was usually present in Lead I in the T_1 or anterior type and a large Q-wave in Leads II and III in the T_3 or posterior type.

Further assistance in the localization of infarcts as well as diagnosis has resulted from the use of precordial leads and exploring leads. Wilson and his associates[5, 6] theoretically and experimentally showed that part of the heart nearest the electrode shows a preponderating influence upon the form of the curve. Consequently[7] in precordial leads the electrical activity of the anterior wall of the heart has a much greater effect on the form of the curve than the electrical activity of the posterior wall. In 1932 they[8] showed two types of precordial curves associated with changes in QRS and T in coronary thrombosis. The first group showed an initial deflection of their curves which is

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upward and of large amplitude and not preceded by a downward deflection, as is ordinarily the case. The T-waves of this group may be negative. In the second group the initial deflection is usually downward and of large amplitude. The T-waves were sharply inverted. The former was associated with anterior wall infarction and the latter with posterior type of infarction. In the same year, however, Wolferth and Wood and their associates[9, 10] were the first to show that precordial leads may display RS-T displacement as well as QRS and T-wave changes in coronary thrombosis when the standard curves are equivocal.

The failure of precordial leads to show striking abnormalities in cases of infarction of the posterior wall is probably due to the fact that the electrode lies at a considerable distance from the damaged area and the intervening healthy muscle exerts a major influence in writing the curve by virtue of its nearness to the electrode. Following the work of Lieberson and Liberson[11] in 1934 and of Brown[12] on the use of esophageal leads, we have attempted to study the electrical events occurring in the region of an infarct of the posterior ventricular wall by means of an electrode placed in the esophagus, i.e., in a position where close contact is obtained with the damaged area without the intervention of a large mass of healthy muscle. For comparison, we have taken precordial leads in cases of posterior infarction, as well as esophageal and precordial leads in cases of anterior infarction and in normal subjects. Records from one subject in each of these groups will be presented.

METHOD

After taking the three standard leads the precordium is explored, using a small German silver electrode (surface area of 1 sq. cm.) as the exploring electrode, and a central terminal attached to the arms and the left leg through three accurately standardized resistances each of 5,000 ohms (Wilson and his coworkers[13]) as the indifferent point. The galvanometer is connected so that relative electronegativity of the exploring electrode results in an upward deflection of the string in all records.* (The string sensitivity in all records was 1 cm. = 1 mv.) The points on which the exploring electrode is placed are as follows: on the fifth rib immediately to the right of the sternum (V_1), on the fifth rib immediately to the left of the sternum (V_2), in the fifth left intercostal space midway between the left lateral sternal line and the midclavicular line (V_3), in the fifth left intercostal space in the midclavicular line (V_4) and on the sixth rib in the left anterior axillary line (V_5).[14] The potential variations of each extremity are then recorded by attaching the exploring wire (right arm) in turn to the electrodes already applied to the right arm (VR), the left arm (VL) and the left leg (VF), the left arm wire from the galvanometer being connected to the central terminal.[14]

Records are finally taken by the esophageal lead. The electrode is of German silver, of circular cross-section, 8 mm. in diameter by 20 mm. in length, and has slightly tapering ends. It is soldered to four strands of insulated copper wire enclosed in a rubber duodenal tube of the Rehfuss type. The right arm wire of the

*When this paper was written, this was the conventional method of recording the laboratory potentials. The nomenclature proposed in Wilson's laboratory[11] had not yet been adopted by the American and British Heart Associations.

galvanometer is attached to the esophageal electrode and the left leg wire to the same indifferent terminal as is used for the precordial leads. The pharynx is cocainized and the electrode passed until it reaches a point 50 to 60 cm. from the incisor teeth, depending on the build of the patient. It is then drawn up 2.5 cm. at a time and records are taken at each interval until a point 25 to 30 cm. from the teeth is reached.

Brown has shown[12] that when the esophageal electrode lies in the region of the auricles characteristic P-waves are written which contain rapid upstrokes analogous to the intrinsic deflection of direct leads. These intrinsic deflections disappear when the electrode is passed below the auriculoventricular groove. Examination of the proximity of the esophagus to the posterior surface of the ventricles in the cadaver

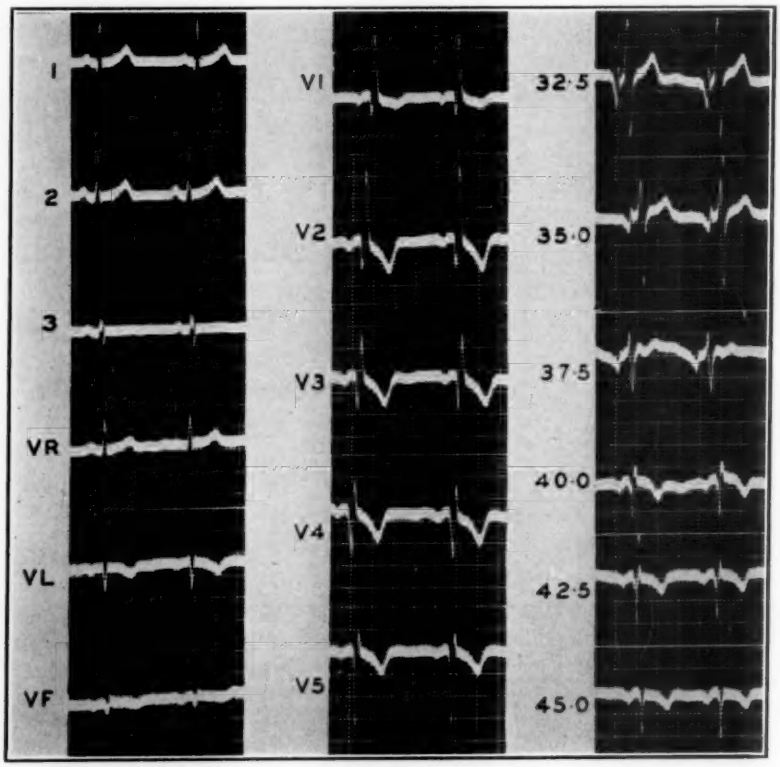

Fig. 1.—Normal subject.

Standard leads 1 2 3 Precordial leads V_1 V_2 V_3 V_4 V_5
Extremity potentials VR VL VF Esophageal leads 32.5, 35, 37.5, 40, 42.5, 45 cm. from the incisor teeth.

(String sensitivity, 1 mv. = 1 cm. in this and the other records.)

shows that close contact is made with the base of the left ventricle, though there may be some divergence lower down. We have therefore selected those tracings obtained from points 5 cm. and more below the lowest level showing characteristic P-waves, as being from the posterior surface of the left ventricle.

RESULTS

1. *Normal Subject* (Fig. 1).—The standard leads show slight left axis deviation, probably due to the transverse position of the heart. This slight axis change is shown also by the presence of a major

downward deflection in the left arm potential curve.[13] Otherwise the extremity potential curves are within the limits of normal set by Kossmann and Johnston.[14] The precordial curves also fall within the normal limits established by these authors.

The esophageal tracings show that characteristic intrinsic auricular deflections are present in the curves taken at 35 cm. and at 32.5 cm. from the teeth. The ventricular deflection is composed of an initial summit followed by an approximately equal depression and a well-marked upright T-wave. The RS-T segment starts close to the isoelectric level but rises steeply into the T-wave. At 37.5 cm. the electrode probably lay close to both auricular and ventricular tissue since the initial ventricular deflection is similar in form to those recorded at higher levels, though the T-wave, diphasic in form, is intermediate between that seen at 35 cm. and that seen at 40 cm.

At and below 40 cm. the P-wave loses all sign of a sharp upstroke, showing that the electrode lay below the auricle and near the ventricular surface. The initial upright ventricular deflection seen at higher levels is replaced by a slight slurring of the major downward deflection, the latter being in turn succeeded by a small summit. The T-wave is directed downward, with the RS-T take-off practically isoelectric.

2. *Myocardial Infarction (Posterior Type).*—Case 1 (Fig. 2). *Standard Leads:* The electrical axis is normal. No Q-deflection is present in Lead I, Q_2 is 1 mm. and Q_3 is 25 per cent of that of the largest QRS deflection in any of the standard leads. Therefore Q_3 satisfies the criteria of Pardee.[15] Neither Q_2 nor Q_3 is large enough to fulfill the conditions suggested by Durant,[16] according to whom Q_2 should be at least 25 per cent of R_2 and Q_3 at least 50 per cent of the largest QRS in any lead. The RS-T segments in Leads II and III are markedly elevated and the T-waves in these leads are inverted, while in Lead I the RS-T segment is slightly depressed and the T-wave is upright. These abnormalities together with the clinical history and examination (see protocol) appear sufficient evidence on which to base a diagnosis of myocardial infarction of the posterior type.

Extremity Potentials: The right arm potential curve *(VR)* shows an initial upright ventricular deflection and a low voltage downward T-wave with slightly elevated RS-T take-off. In the left arm curve (VL) there is an initial depression followed by a summit, a considerably elevated RS-T segment and a downward T-wave, while the left leg curve (VF) shows an initial summit followed by a larger depression, a well-marked upright T-wave and a depressed RS-T interval. It will be noticed that Lead VL resembles Lead III in contour.

Precordial Leads: In these leads (particularly V_3, V_4 and V_5) the ventricular complex is initiated by a deep downward deflection. The

RS-T segment is elevated and the T-wave is directed downward and of large size. These are in keeping with the abnormalities shown by the standard leads.

Esophageal Leads: At 42.5 and 37.5 cm. the presence of sharp rapid auricular deflections indicates that the electrode was close to the auricular surface. At 42.5 cm. the ventricular deflection does not differ in general form from those recorded from points lower down, but at 37.5 cm. it differs considerably. After a very small downward

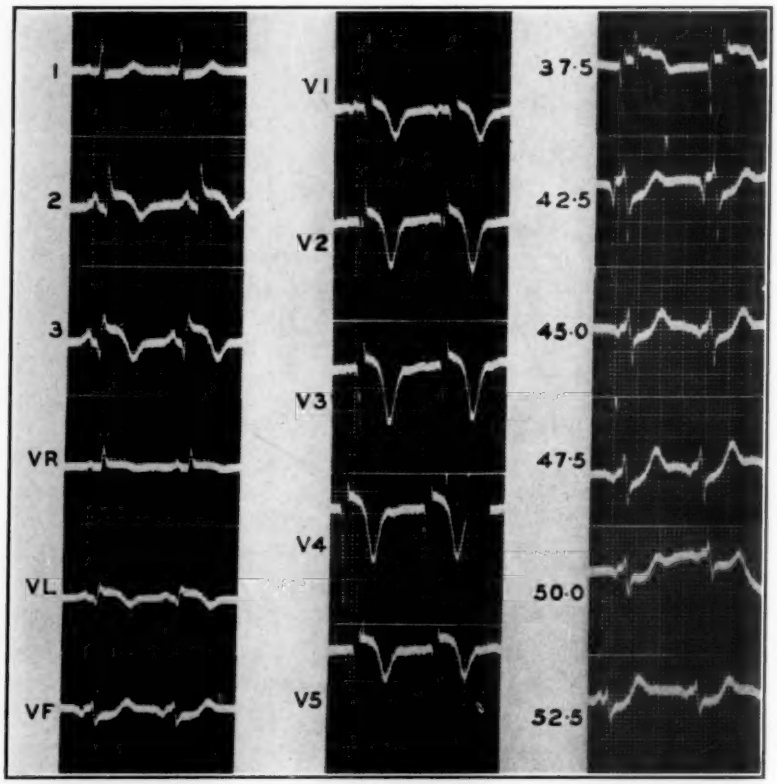

Fig. 2.—Case 1. Posterior myocardial infarction.

Standard leads 1 2 3
Extremity potentials VR VL VF
Precordial leads V_1 V_2 V_3 V_4 V_5
Esophageal leads 37.5, 42.5, 45, 47.5, 50, 52.5 cm. from the incisor teeth.

wave there is a relatively large upright deflection, smaller downward and upright waves, an elevated RS-T segment and an inverted T-wave.

The curves taken from juxtaventricular positions (namely 45 to 55 cm. from the teeth) show somewhat low amplitude of the initial ventricular deflection which begins with a small summit followed by a slow downward deflection, indicating relative electropositivity of the exploring electrode. After the next short but more rapid upward movement, which probably represents the intrinsic deflection, there

is a markedly depressed RS-T interval and an upright T-wave. By comparison there are marked similarities of the contours of these esophageal ventricular deflections to those of the left leg (VF).

3. *Myocardial Infarction (Anterior Type).*—Case 2 (Fig. 3). *Standard Leads:* The electrical axis is normal. Q-waves are present in Leads I and II. There is no Q-deflection in Lead III. The amplitude of Q_2 is 25 per cent of that of R_2 and the amplitude of Q_1 is greater than 1 mm. and more than one-fifth as large as the largest R-wave in any

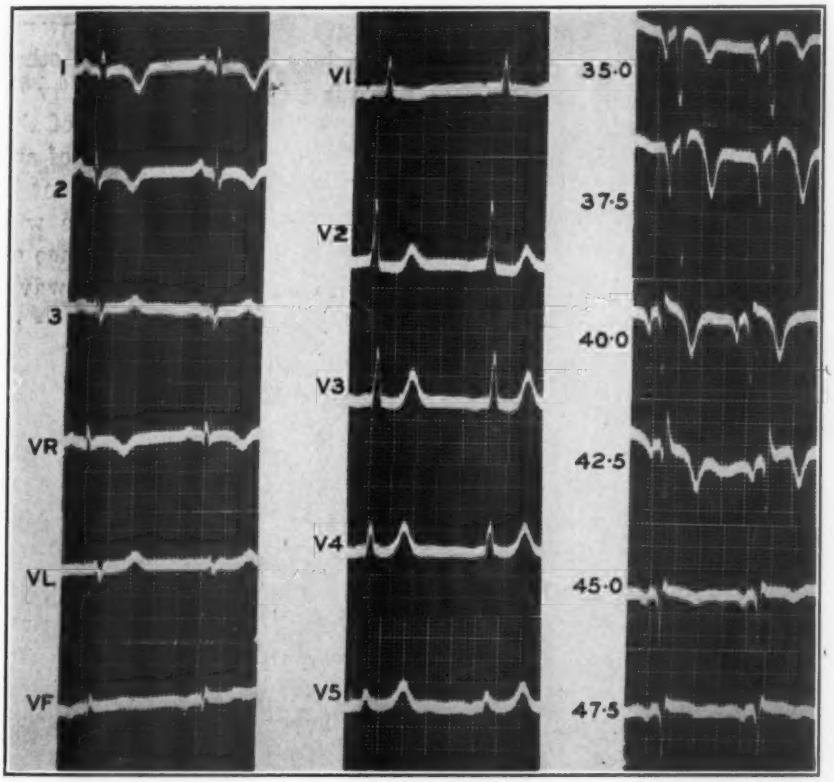

Fig. 3.—Case 2. Anterior myocardial infarction.

Standard leads 1 2 3 Precordial leads V_1 V_2 V_3 V_4 V_5
Extremity potentials VR VL VF Esophageal leads 35, 37.5, 40, 42.5, 45, 47.5 cm. from the incisor teeth.

standard lead; R_1 is less than 5 mm. high. The RS-T segment is curved upward in Leads I and II and the T-waves are inverted, while in Lead III the RS-T segment is isoelectric and flat and the T-wave is upright. These abnormalities together with the clinical history and examination (see protocol) appear sufficient evidence on which to base a diagnosis of myocardial infarction of the anterior type. It is further noted that except for the presence of inverted T_2, Durant's criteria[16] for Q_1 T_1 type curves are satisfied.

Extremity Potentials: The right arm curve (VR) consists of a small initial downward, a well-marked upward, and another small downward wave, an inverted T-wave with a nearly isoelectric and upwardly convex RS-T take-off. The left arm curve (VL) shows small upward and larger downward deflections with an upright T-wave rising from the isoelectric level. In the left leg tracing (VF) there are again small upward and downward waves, but the latter are followed by a larger summit. The T-wave is small and upright and the take-off is isoelectric. VR resembles Lead I and VL Lead III.

Precordial Leads: These show an absence of the initial downward deflection. In V_2 the RS-T segment is slightly depressed but in other positions, isoelectric. In V_3, V_4, V_5 there is a downward convexity of this segment. The T-waves are upright from points to the left of the sternum. These abnormalities are consistent with the diagnosis of anterior infarction. In the routine apical lead records of this case made immediately and for some time after the acute episode, there was marked depression of the RS-T segment, in addition to the absence of an initial downward deflection and the presence of an upright T-wave.

Esophageal Leads: The characteristic auricular deflection appears at 37.5 and 35 cm. and is well marked until the 30 cm. level is reached. At these levels the ventricular complex, beginning with a small summit, is chiefly composed of a large downward wave. The RS-T segment is elevated and rounded and the T-wave directed downward. It is also observed that when the electrode lies over the lower part of the auricle and the upper part of the ventricle, between 37.5 and 42.5 cm., the T-wave is exceptionally deep.

In the curves obtained from juxtaventricular points (40, 42.5, 45, 47.5 cm.) the ventricular deflection consists of a well-marked downward swing with slight initial slurring followed by a summit, an elevated RS-T segment and a downwardly directed T-wave. The latter curves (45 and 47.5 cm.) somewhat resemble the leg lead (VF) except in amplitude.

DISCUSSION

Leads of the type used in this study are theoretically unipolar and represent the potential variations of the exploring electrode with respect to an indifferent central terminal, the potential of which remains at zero throughout the cardiac cycle. When the exploring electrode is placed in close proximity to the heart the resulting curve records, more or less faithfully, the potential changes occurring at the adjacent epicardial surface. Those esophageal curves of Case 1 and those precordial curves of Case 2 in which the exploring electrode was close to the infarcted region are similar in general outline. In both cases the RS-T segment is displaced downward and the T-deflection is sharply upright. In the case of the QRS deflection the resemblance is somewhat less striking, but both sets of curves display a con-

spicuous summit at the onset of the QRS interval, indicating initial negativity of the exploring electrodes. In other words, the initial downward movement present at the beginning of the QRS interval in normal precordial curves and in the curves obtained from the lesser levels of the esophagus in normal subjects is absent. The initial summit in question is much larger in the precordial curves (Case 2) than in the esophageal curves (Case 1); in the latter it is followed by a conspicuous downward movement. A similar summit occurs in the first three esophageal curves of our normal subject (Fig. 1), but not in the others from lower levels. No initial summit occurs in the esophageal curves at the ventricular level of Case 2, in the precordial curves of Case 1, or in the precordial curves of the normal subject.

In electrocardiographic studies of experimental infarcts produced in dogs by coronary ligation, Wilson and his associates[17] have shown that the curves, obtained by leading directly from the surface of infarcts which are composed of dead muscle and extend completely through the ventricular wall, closely resemble those obtained by leading directly from the ventricular cavity beneath the infarcted region. In this case the dead muscle of the infarct appears to act as a window or opening in the ventricular wall, which permits the potential variations of the ventricular cavity to be transmitted to the epicardial surface. The valvular orifices at the base of the heart act in the same way, and leads from points in close proximity to and facing these orifices display a large initial upward or minus deflection at the beginning of the QRS group similar to that seen in leads from the ventricular cavity or from the surface of an infarct. This, no doubt, explains the occurrence of an initial summit in leads from the auricular levels of the esophagus in normal subjects (Fig. 1).

In direct leads from experimental infarcts which involve only the subendocardial layers of muscle the initial summit is smaller. It does not constitute the sole QRS deflection, as it does when the infarct extends completely through the ventricular wall, but is followed by a conspicuous downward movement which terminates in a sharp upward movement or intrinsic deflection of subnormal amplitude. The relatively small size of the initial summit and the deep downward movement following it in the esophageal curves of Case 1 (Fig. 2) suggest that the infarct did not involve the entire thickness of the ventricular wall. The anterior infarct of Case 2, on the other hand, did apparently penetrate the ventricular wall if we may judge by the form of the corresponding precordial leads, in which a large initial summit is the sole deflection of the QRS group.

In animal experiments[19] pronounced RS-T displacement in the downward or plus direction occurs in direct leads from the surface of the infarct for a few hours immediately following coronary ligation. It disappears when the injured muscle dies or recovers. Wilson and his associates[20] have shown in experiments on the turtle heart

that in direct leads from the side of the heart opposite the injured region the RS-T displacement is in the upward or negative direction. It will be noted that in Case 1 the leads from the lower levels of the esophagus show conspicuous downward displacement of the RS-T segment, whereas in the precordial leads and in the first esophageal lead (at 37.5 cm.) the RS-T displacement is in the upward direction. The presence of marked RS-T displacement in this case suggests that the infarction is still in an early stage and that much of the damaged muscle is still alive. The small size of the initial QRS summit of the esophageal leads may be due in part to this cause.

In direct leads from experimental infarcted animal hearts striking T-wave changes of the type seen in human coronary occlusion are compared to leads from the marginal portion of the infarct.[17, 18] These T-wave changes appear to depend upon a disturbance in damaged but not fatally injured muscle, which alters the retreat of the exciting process. When the exploring electrode is not in contact with the epicardial surface but merely close to it, the curve obtained represents the average of the potential variation occurring over a considerable area. It may be for this reason that precordial leads and esophageal leads frequently yield curves which combine features seen in direct leads from the central portion of an experimental infarct with features peculiar to direct leads from the marginal portion. In other words, fully developed QRS changes and fully developed T-wave changes may be present together in precordial (Fig. 3) or in esophageal leads.

CASE PROTOCOLS

CASE 1.—E. E., a white male, aged fifty-nine, entered the Boston City Hospital on Dec. 15, 1936 and died forty-eight hours later. He had suffered from malaria when in the Philippine Islands in 1900 to 1901 and had been treated with quinine for seven years. Though high blood pressure had been discovered five years previous to admission, he had been well until the day before, when he had short attacks of substernal pain which radiated to the left arm and were accompanied by a feeling of constriction around the chest, difficulty in breathing, and sweating. Two of these attacks occurred during the day while he was working and the third awakened him during the night. Each attack lasted for about two to five minutes. While walking to work on the day of admission he again suffered from the same symptoms, which were slightly but very temporarily relieved by nitroglycerine. The pain and constriction in the chest became very severe and he vomited and felt faint. An injection of morphine after admission to the hospital was necessary to provide relief.

Examination revealed a slightly cyanosed man who (after morphine) was not uncomfortable. The cardiac apex was found to be in the fifth intercostal space 1 cm. outside the midclavicular line. The cardiac rhythm was regular and the rate 90. The heart sounds were indistinct, but no murmurs or pericardial friction were heard. The blood pressure was 140/96. There was no cervical venous distension and no hepatic enlargement, though a few coarse râles were heard in both lungs. There was no peripheral edema. The temperature on admission was 97.6° F.

Laboratory Data.—The urine contained a small trace of albumin. The hemoglobin and red blood cell count were normal. The leucocytes were increased to 21,250 per

cubic millimeter on the day of admission but fell to 7,200 on the third day. Blood nonprotein nitrogen was 29 mg. per cent. The Hinton test on the blood was negative for syphilis. The corrected sedimentation rate was 34 mm. (Wintrobe method) in one hour on December 15, and 13 mm. on December 17.

Course.—The temperature rose to 100° F. on the second day and to 100.2° on the third day. Throughout the second day and until the early afternoon on the third day he felt perfectly comfortable. The esophageal electrode was swallowed on the second day without discomfort or any untoward sign. At 2:00 P.M. on the third day, while he was consulting his lawyer, he suddenly became acutely dyspneic and cyanosed and died within five minutes. Permission for autopsy was refused. No digitalis was administered throughout the course of the illness.

CASE 2.—B. C., a white male, aged forty-nine, entered the Boston City Hospital on Jan. 15, 1937, and was discharged on March 6, 1937. One month before admission he first suffered from short attacks of dull squeezing pain in the chest, brought on by exercise and relieved by rest. These became more frequent ten days before admission. On the morning of the day of admission he was attempting to rise from bed when he was seized by a very severe constricting pain in the chest which became worse, caused nausea and vomiting and necessitated two injections of morphine before he was brought to hospital.

Examination revealed an acutely ill man complaining of precordial pain. The cardiac apex was found to be in the fifth intercostal space, 10 to 11 cm. to the left of the midsternal line. The cardiac rhythm was regular and the rate 100. The heart sounds were faint but no murmurs, gallop rhythm, or pericardial friction were heard. The blood pressure was 140/90. Cervical venous distension, peripheral edema, and hepatic enlargement were absent, but a few moist râles were heard at the left lung base. The temperature on admission was 97° F.

Laboratory Data.—The urine contained a small trace of albumin; hemoglobin and red cell count were normal. The leucocytes were increased to 11,500 per cubic millimeter, but returned to normal on the third day. The blood nonprotein nitrogen was 30 mg. per cent. The corrected sedimentation rate (Ernstene method) was 0.3 mm. per minute. The Hinton test on the blood was negative for syphilis. X-ray cardiac measurements, made two weeks after admission, were as follows: To the left of the median line 11.5 cm., to the right 6 cm., internal diameter of the thorax 33.5 cm. and great blood vessels 8 cm.

Course.—The temperature rose on the second day and remained at 101° F. for three days. The pulse rate fell gradually to about 80. On the fourth day a pericardial friction rub was heard at the right sternal border in the fourth intercostal space which disappeared on the following day. The blood pressure fell to 94/50 on the tenth day, and on discharge was 100/60. Some precordial discomfort remained for three weeks but thereafter the convalescence was uneventful. The esophageal electrode was swallowed on February 23 without discomfort or any untoward sign. No digitalis was administered throughout the course of the illness.

SUMMARY

1. Standard leads, unipolar extremity leads, unipolar precordial leads, and unipolar esophageal leads were employed in a normal subject, in a case of infarction of the posterior wall of the heart and in a case of infarction of the anterior wall of the heart.

2. These curves have been analyzed and compared and it has been found that the precordial electrocardiograms characteristic of anterior infarction resemble the esophageal electrocardiograms characteristic of posterior infarction, and vice versa.

3. In general the curves here presented provide evidence that the potential variations occurring at the epicardial surface of myocardial infarcts in man are similar to those which occur at the epicardial surface of infarcts produced in animals by coronary ligation.

We are deeply indebted to Dr. Frank N. Wilson for his very helpful criticism.

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COMPARATIVE EFFECTS OF WATER BATHS AND MUSTARD BATHS AT VARYING TEMPERATURES ON THE RATE OF PERIPHERAL BLOOD FLOW IN MAN

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THE ever increasing number of reports in medical literature of clinical and experimental studies of the peripheral vascular system in man point to a growing interest among both clinicians and experimentalists in variations in rates of peripheral blood flow in both physiologic and pathologic states. This interest has been stimulated largely by the development of simplified and practicable apparatus for recording skin surface temperatures and for photographing the capillaries of the skin at the nail fold; excellent modifications of these methods have been developed by Wright and Duryee.[1] Application of these procedures to the clinical study of the peripheral vascular system in several peripheral circulatory clinics has revealed frequent and marked depression of the skin surface temperature and stoppage of blood flow in the capillaries of the extremities in a variety of pathologic states and in apparently normal subjects in response to drugs and some foods and after smoking tobacco.[2, 3, 4] Although results obtained by these procedures should be accepted as qualitative indications only, not as quantitative measurements, they emphasize both the frequency of depressions in peripheral blood flow and the need of a simple and readily available method for prevention of, and relief from, disturbances of the peripheral blood circulation.

Wright and Duryee,[5] in their excellent review of the present knowledge concerning human capillaries, point out that the capillary bed is responsive to chemical influences by local reactions, usually by dilatation (only in special or pathologic cases by general reactions) and to nervous stimulation, usually by constriction, over the body as a whole. It is, therefore, likely that beyond the arterioles the capillaries and venules function actively, thereby participating directly in vascular reactions. Although it has long been known that mustard baths improve the peripheral circulation, Mattill[6] in his review of the literature on hydrotherapy cites only one reference to mustard baths in which it had been shown that the addition of mustard to a bath at neutral temperatures increased the oxygen consumption and the carbon dioxide output by 25 per cent although the bath alone had no demonstrable influence on metabolism.

The experiments herein reported were undertaken to determine quantitatively the effects of adding mustard to water baths at temperatures between 25° C. and 40° C. upon the rate of peripheral blood flow in the hand or foot immersed in the bath. With this objective in mind, com-

parisons have been made of the effects of mustard baths and water baths at similar temperatures. Lampson[7] applied Freeman's modification of the method of Hewlett and van Zwaluwenberg[8] to a quantitative study of the vasoconstriction induced by smoking. This procedure was adopted in the experiments described below. In order to observe changes in rates of blood flow in the foot, a plethysmograph, which accommodates the foot comfortably, was constructed. Fig. 1 gives the sketch of this apparatus and the method of insertion of the foot and of supporting the leg.

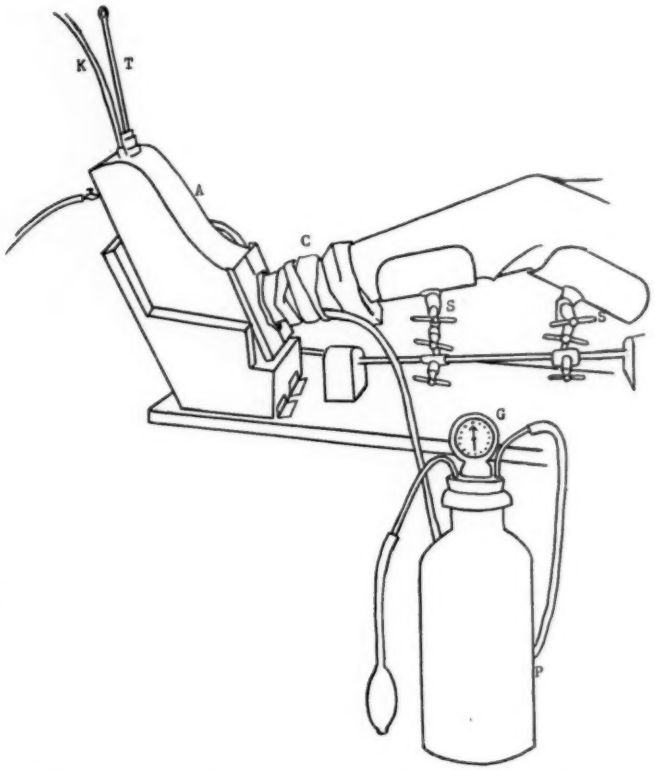

Fig. 1.—*A*, the brass plethysmograph into which the foot has been inserted.
T, thermometer inserted into the bath with the plethysmograph.
K, rigid rubber tubing leading from the plethysmograph to the Brodie bellows.
C, cuff to shut off return of venous blood from foot.
P, pressure bottle.
G, pressure gauge.
SS, supports for leg.

Three normal men and six normal women, whose ages varied from 21 to 32 years, served as experimental subjects.

In all experiments the room temperature was maintained between 18° and 20° C. Before the tests, the subjects were given periods of complete rest varying from thirty to sixty minutes. During the experimental period the subjects reclined at rest on a couch provided with a comfortable back rest. Either the right arm or the right foreleg was supported on a horizontal plane above the level of the heart.

Hewlett and van Zwaluwenberg have stated that in favorable cases the error of the method does not exceed 20 per cent. In the experience of the authors, the probable experimental error of the method is ±15 per cent with the hand plethysmograph and ±12 per cent with the foot plethysmograph. These have been estimated from the mean average deviations in the rate of peripheral blood flow during control periods in all experiments, of which the average results have been summarized in Table I.

TABLE I

VARIATIONS IN RATES OF PERIPHERAL BLOOD FLOW IN EXTREMITIES OF EXPERIMENTAL SUBJECTS DETERMINED AT DIFFERENT TIMES

SUBJECT	NUMBER OF DETERMINATIONS	LENGTH OF EXPERIMENTAL PERIOD IN MINUTES	EXTREMITY USED	PERIPHERAL BLOOD FLOW AS INCREASE IN VOL. OF EXTREMITY C.C. MIN.			AVERAGE RATE OF INFLOW OF BLOOD PER 100 C.C. HAND OR FOOT PER MINUTE
				MAXIMUM	MINIMUM	AVERAGE	
R.B.	6	35	hand	39	35	36.3	6.7
	4	17	hand	26	22	24.6	4.5
	3	25	hand	25	23	24.4	4.5
L.L.	3	15	hand	10	8	8.8	3.2
	5	30	hand	7	5	5.3	1.9
	5	30	hand	13	8	11.6	3.3
D.L.	6	30	hand	11	8	9.3	2.3
	4	16	hand	6	5	5.6	1.4
	6	15	hand	19	11	14.0	3.5
M.L.H.	6	25	hand	34	29	32.4	7.8
K. B.	4	30	hand	9	8	8.4	2.4
A.S.	5	52	hand	13	8	9.6	3.0
	6	55	hand	28	20	24.0	7.5
C.K.	7	46	hand	20	10	17.5	3.7
	4	26	hand	20	8	12.6	2.6
	5	27	hand	37	27	31.8	6.1
N.K.	9	41	foot	23	17	21.1	3.1
	9	26	foot	18	12	14.5	2.0
L.L.	9	32	foot	22	12	17.3	2.6
	10	50	foot	34	23	27.9	4.2
C.K.	4	31	foot	20	10	14.0	1.3
	3	24	foot	17	11	13.2	1.1
	6	45	foot	17	12	15.6	1.4
	6	40	foot	32	17	28.2	2.5

Table I presents data for rates of peripheral blood flow either in the hands or the feet of the experimental subjects determined during control periods on different days but under similar experimental conditions. Variations from 50 to 150 per cent have been found in the results obtained at different times for any one subject. Hewlett and van Zwaluwenberg have reported equally variable results for the same individual at different times. Since only well-trained subjects were employed in these experiments and they remained at rest during the experimental periods and since the temperature within the plethysmograph was main-

tained within ±1° C. and variables in the environment were excluded, it seems that the factors producing the variations noted are probably beyond the control of the experimenter. In order to exclude variations in peripheral blood flow when determined on different days, the effects of

TABLE II

COMPARATIVE EFFECTS OF BATHS IN WATER AND IN MUSTARD WATER UPON THE RATE OF PERIPHERAL BLOOD FLOW

SUBJECT	EXTREMITY	BATH	AVERAGE TEMPERATURE OF BATH °C.	EXPERIMENTAL PERIOD MINUTES	NUMBER OF DETERMINATIONS	RATE OF PERIPHERAL BLOOD FLOW AS INCREASE IN VOLUME OF EXTREMITY—C.C. PER MINUTE		
						MAXIMUM	MINIMUM	AVERAGE
L.L.	hand	Water	37.0	15	3	10	8	8.8
		0.5 per cent mustard	37.0	45	7	22	14	18.0
D.L.	hand	Water	35.0	16	4	6	5	5.6
		0.6 per cent mustard	35.0	46	8	11	5	8.3
C.K.	hand	Water	34.9	30	6	58	29	40.5
		0.6 per cent mustard	35.1	34	4	68	56	61.2
L.L.	foot	Water	36.6	50	10	31	23	27.9
		0.6 per cent mustard	36.8	55	9	47	36	41.5
L.L.	foot	Water	35.9	32	9	22	12	17.3
		0.6 per cent mustard	36.1	46	7	48	33	42.7
N.K.	foot	Water	35.0	41	9	23	17	21.1
		Water	40.5	33	6	50	40	44.9
		0.6 per cent mustard	40.8	31	6	57	46	50.9
N.K.	foot	Water	35.5	26	9	18	12	14.5
		Water	38.2	49	9	42	21	30.7
		0.6 per cent mustard	38.1	66	9	50	38	42.2
C.K.	foot	Water	34.9	49	5	93	29	38.4
		0.6 per cent mustard	35.0	60	4	65	43	50.6
C.K.	foot	Water	39.8	33	5	82	61	68.2
		0.6 per cent mustard	39.8	36	5	114	92	100.6
J.D.	foot	Water	39.9	31	5	108	82	99.6
		0.6 per cent mustard	39.9	31	7	152	128	139.7

mustard baths have been determined by comparing the rates of blood flow into the hand or foot, immersed in mustard baths, with rates found on the same day during control periods immediately preceding the mustard baths. During the control periods the hands or feet of the subjects were immersed in water maintained at a temperature similar to that of the mustard bath.

In Table II are reported results of three experiments made on hands and seven experiments on feet showing the comparative effects of water and mustard baths upon the rate of blood flow in these extremities at temperatures between 35° C. and 40° C. In the preparation of the mustard baths, enough mustard was weighed out to give a final concentration of 0.6 per cent mustard. This was stirred well into a small volume of water for about two minutes and was then added to the total volume of water to be used in the bath. In all experiments the same volume of the hand or foot was inserted into the plethysmograph in the water bath as in the mustard bath periods. At the end of the water bath period the water was withdrawn from the plethysmograph and replaced by the mustard solution. Results are presented in Table II for rates of blood flow, as increases in volumes of the hand or foot, calculated in cubic centimeters per minute, for the total volume of the hand or foot inserted into the plethysmograph. Throughout the periods during which determinations of rates of blood flow were made, the temperatures of the fluids within the plethysmograph were maintained constant within ±0.4° C.

In all experiments, immersion of the hand or foot in a mustard bath produced an increase in the rate of flow of blood into these extremities above the levels found for the water baths under like experimental con-

TABLE III

COMPARATIVE EFFECTS OF WATER BATHS AND MUSTARD BATHS AT VARYING TEMPERATURES UPON THE PERIPHERAL BLOOD FLOW IN EITHER THE HAND OR THE FOOT

SUBJECT AND PART IMMERSED IN BATH	BATH	AVERAGE TEMPERATURE °C.	TIME IN MINUTES	NUMBER OF DETERMINATIONS	AVERAGE RATE OF BLOOD FLOW C.C. PER MINUTE PER 100 C.C. EXTREMITY	
C. K.	Water	25.0	44	5	2.0	±0.36
		30.1	46	7	3.7	±0.65
Hand		34.9	29	6	8.6	±1.93
		39.7	39	4	15.5	±0.62
		44.8	27	4	17.1	±1.15
	Controls in water	25.0	17	3	2.2	±0.66
		29.9	26	4	2.6	±0.80
	0.6 per cent mustard	25.2	32	4	1.9	±0.35
		30.2	34	4	9.3	±0.97
		35.1	34	4	12.6	±0.67
		40.0	23	4	14.5	±1.97
C. K.	Water	25.3	31	4	0.9	±0.07
		30.2	40	4	1.3	±0.27
Foot		34.9	49	5	3.5	±0.42
		39.8	34	5	7.9	±0.98
		44.8	22	5	14.8	±0.58
	Controls in water	25.0	16	3	0.9	±0.13
		29.9	24	3	1.1	±0.16
	0.6 per cent mustard	25.1	25	4	0.9	±0.15
		30.3	34	4	1.6	±0.17
		35.0	26	4	4.1	±0.57
		40.0	25	4	13.2	±0.80

ditions. The average rates of blood flow into the hand, when immersed in mustard, were from 48 to 125 per cent (average 74 per cent) greater than when immersed in water. In the seven experiments on the foot, the rates of blood flow were from 11 to 146 per cent (average 51 per cent) greater with mustard baths than with water baths.

Comparative effects of exposing the surface of the skin to temperatures below and above the average skin surface temperature upon the

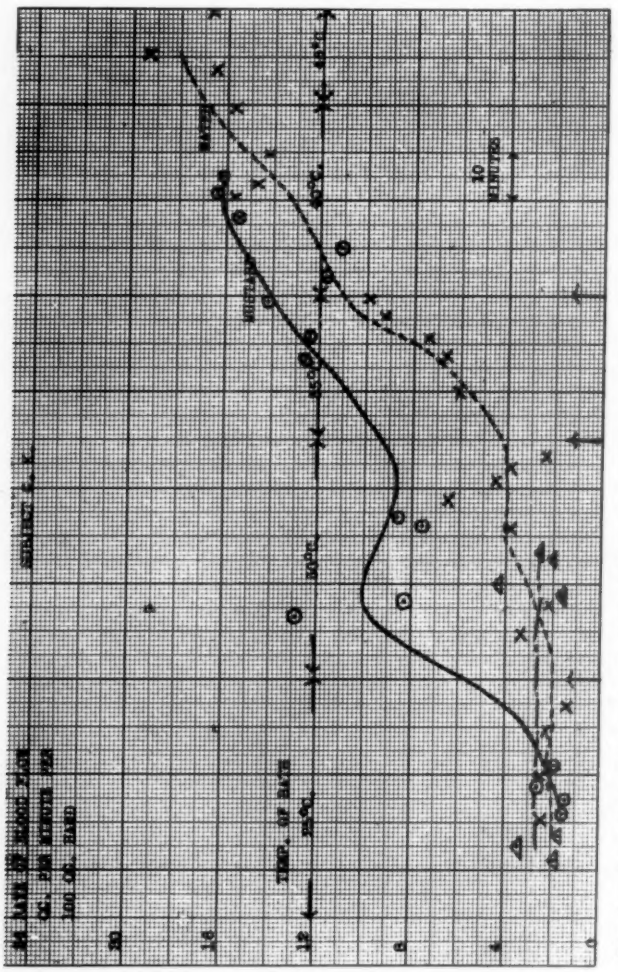

Fig. 2.—Comparative effects of water baths and mustard baths at varying temperatures upon the rate of peripheral blood flow in the hand.

rate of blood flow in the hand and in the foot have been observed in two series of experiments of which the results are reported in Table III. Temperatures of the baths in the plethysmographs between 33 and 35° C. were found to approximate closely the subjects' estimates of their skin temperatures. When the temperatures of the baths were maintained within this range, the subjects noted no differences between the temperature of the bath and the temperature of their skins.

Determinations of rates of blood flow were begun only after the extremity had been adjusted to the temperature after immersion for from 10 to 15 minutes. The comparative experiments with water and with mustard baths were carried out on different days. However, on the days of the experiments with mustard, control periods preceded the use of the mustard baths. In these control periods, either the hand or the foot was immersed in water at 25° C. and 30° C. Results obtained during

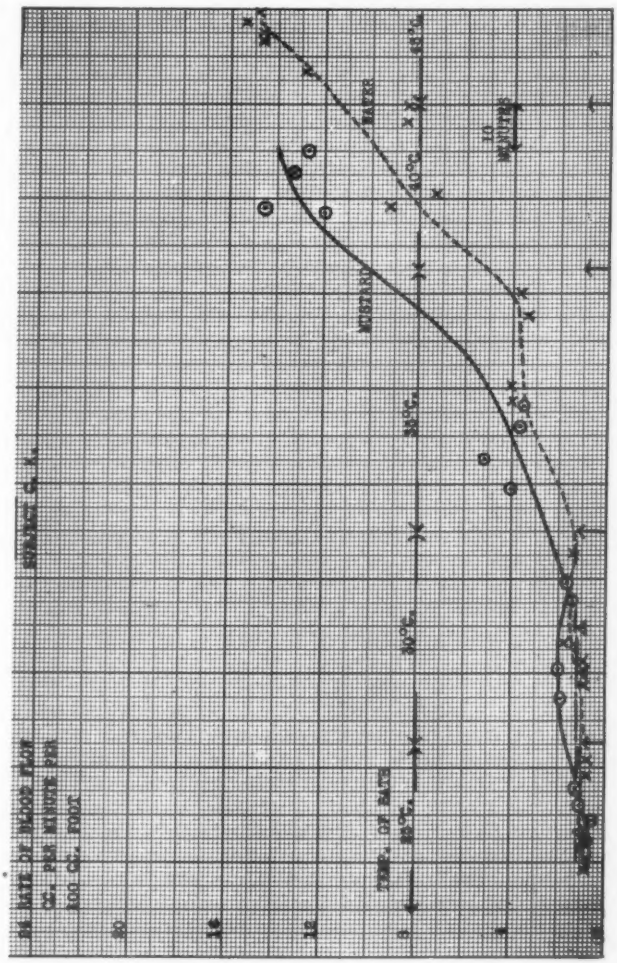

Fig. 3.—Comparative effects of water baths and mustard baths at varying temperatures upon the rate of peripheral blood flow in the foot.

these control periods confirm the findings for the water baths at these temperatures noted on the days of the water bath experiments.

Cooling the surface of the skin of the hand by immersing it in water at 30° C. decreased the average rate of blood flow to 43 per cent, and cooling it in water at 25° C., to 23 per cent of the average level at 35° C. Elevating the temperature of the water bath to 40° C. increases the rate of flow of blood into the hand by 80 per cent. At a temperature of 25° C. there was noted no significant difference between the effects of

the water bath and the effects of the mustard bath upon the rate of peripheral blood flow into the hand, but at 30° C. the average rate of blood flow into the foot is 3.5 times the average rate in the mustard bath as compared with the water bath at 30° C. on the same day, and 2.5 times that of the day of the water bath experiments. At 35° C. the difference between the effects of the mustard bath and the water bath were less marked. At this temperature the average rate of blood flow in the hand immersed in the mustard bath is 46 per cent greater than the average rate in the water bath. At 40° C. the difference between the average rates for the mustard bath and the water bath are within the limits of experimental error of the method. Fig. 2 summarizes these data as curves showing changes in rates of blood flow in the hand immersed either in a water bath or in a mustard bath at temperatures varying from 25° C. to 40° C. for the mustard bath and from 25° C. to 45° C. for the water bath.

Similar responses in the peripheral blood flow to changes in the temperature of the baths were noted in experiments on the foot. Cooling the surface of the skin of the foot by immersing the foot in baths at 25° C. depresses the rate of blood flow into the foot to 25 per cent of the average rate for the water bath at 35° C. At 30° C. and 35° C. in these experiments, the mustard bath did not significantly increase the rate of blood flow above the average levels for the water bath. However, when the foot was immersed in the mustard bath at 40° C., the average rate of peripheral blood flow into the foot was 67 per cent greater than the average rate for the water bath at the same temperature.

Results of these comparative experiments with water baths and mustard baths on the foot are presented in the curves of Figure 3. Significant differences between the effects of the water bath and mustard bath appear only at a temperature of 40° C. In the mustard bath at this temperature, the rates of flow of blood into the foot are approximately equivalent to the rates determined in the water bath at 45° C.

SUMMARY

1. Mustard baths* containing 0.6 per cent mustard have accelerated the rate of peripheral blood flow into both hands and feet above the levels found for water baths at similar temperatures, between approximately 35° C. and 40° C. In three experiments on the hand the average increase found for the mustard baths above the levels of the water baths was 74 per cent. In seven experiments on the foot, the average increase found for the mustard baths above the levels for the water baths was 51 per cent.

2. Cooling the surface of the skin of either the hands or the feet, by immersion in water at 30 to 25° C., depresses the rates of peripheral

*The authors wish to take this opportunity of thanking the manufacturers of Colman's mustard for supplying the dry mustard used in these experiments.

blood flow to levels of 40 to 25 per cent of the average levels at the average normal temperature of the skin.

3. In comparative experiments at 25° C. on one subject there was noted no significant difference between the effects of mustard baths and water baths upon the rates of peripheral blood flow in the hands. However, adding mustard to the water at 30° C. markedly increased (150 per cent) the rate of peripheral blood flow in the hand above the level for the water bath. At 35° C. a smaller difference was noted (46 per cent), and at 40° C. no significant difference was found between the effects.

4. At temperatures of 25 and 30° C. the mustard bath did not affect the rate of peripheral blood flow in the foot more than the water bath. At temperatures between 35 and 40° C., the mustard bath did increase the rate of blood flow from 17 to 69 per cent above the average rates for water baths at these temperatures.

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THE ELECTROCARDIOGRAPHIC CHANGES FOUND IN 22 CASES OF CARBON MONOXIDE (ILLUMINATING GAS) POISONING*

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IN A PREVIOUS investigation Shillito, Drinker, and Shaughnessy[4] (1936) described certain neurologic sequelae in carbon monoxide poisoning. The other great field upon which attention has been focused in this condition is that of the cardiovascular system. There have been a number of electrocardiographic studies on experimentally asphyxiated animals, but only in a single instance have the electrocardiographic findings in poisoned patients been reported. Therefore, it seemed worth while to study a series of such cases by means of the electrocardiograph. The twenty-two cases upon which this paper is based are typical of those admitted to a city hospital.

All of the patients were admitted directly to the emergency ward upon their arrival at the hospital. However, before being removed from the scene of their asphyxiation, they had been treated with 7 per cent carbon dioxide and 93 per cent oxygen inhalations for varying lengths of time. Thus, when these patients were first seen by the clinicians, they were no longer in a state of asphyxiation, large experience having demonstrated that only innocuous amounts of carbon monoxide remain in the blood after the routine inhalation treatment given either by the gas company or police emergency squad. The physiologic abnormalities which may be present in such patients upon admission to the hospital, and thereafter, should be regarded as the sequelae of anoxemia rather than as symptoms of residual anoxemia. We had hoped to be able to obtain some electrocardiograms upon profoundly asphyxiated patients (i.e., before they had received any carbon dioxide and oxygen inhalations), but because of practical difficulties this attempt had to be abandoned. Therefore the electrocardiograms in this series represent the cardiac status following, rather than during, the period of anoxemia.

Table I summarizes the relevant facts concerning these cases. It should be understood that in calculating the duration of unconsciousness, no attempt has been made to estimate how long the patients were unconscious preceding discovery. Also, the time is conservative from

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the standpoint of recovery of consciousness, as many patients later had no recollection of experiences occurring at a time when they had been regarded as conscious.

In Table II are listed the changes found in each electrocardiogram, the time after admission at which it was taken, and the patient's blood pressure at that time. Only positive findings are recorded.

It was possible to locate only seven of the surviving twenty patients for a follow-up after they had left the hospital. The electrocardiographic findings thus obtained are incorporated in Table II.

Inasmuch as the clinical course of this group of cases was rather stereotyped, we are presenting brief histories of only three typical cases.

CASE 3.—The patient was a fifty-four-year-old white male who was found unconscious in a gas-filled room. He received inhalations for forty minutes and was said to have been conscious at the end of the treatment. On admission he was confused and disoriented, and appeared markedly dehydrated. Later the history was obtained that he had been on a four-day drinking bout.

The admission temperature was 101.8° F., pulse 110, blood pressure 130 systolic, 90 diastolic. The lungs were clear except for occasional wheezes. The heart was not enlarged. The sounds were of poor quality and the rhythm was regular. There were no signs of cardiac failure. Peripheral arteries were moderately thickened.

An electrocardiogram taken two and one-half hours after admission showed a regular rhythm, with a rate of 100 per minute. Noteworthy changes were rather low P-waves in all leads, a flat T-wave in Lead I and an upright T-wave in Lead IV.*

For the first two days after admission the patient was confused and drowsy but was mentally clear thereafter. During this time and for several more days he ran a low-grade fever, the result of a mild bronchitis. An electrocardiogram taken on the second hospital day showed more normal P-waves. The T-waves were as on the preceding day. An electrocardiogram on the third day again showed rather low P-waves, as on the first day. A fourth electrocardiogram, taken on the tenth day, showed flat P-waves in Lead II, inverted P-waves in Lead III. In the first lead T-waves were inverted, and in the second lead were very low with a slight late rise. T_4 was again upright.

The patient went home on the fourteenth day, free from complaints. It was impossible to locate him later for further study.

CASE 7.—The patient was a sixty-five-year-old white male chronic alcoholic. When found, approximately one hour before admission to the hospital, he was lying completely unconscious in a gas-filled room with one unlighted stove burner blowing gas. The breathing was reported as slow and gasping, the lips blue, and the body cold. Artificial respiration was applied for eight minutes before the arrival of the Emergency Squad, at which time 7 per cent oxygen and 93 per cent carbon dioxide inhalations were started. After thirty minutes the condition of the patient was improved sufficiently for him to be removed by ambulance to the hospital, inhalations being continued there for fifteen minutes.

On admission the patient was somewhat irrational. The temperature was 96° F., the pulse 124, and the blood pressure 120 systolic and 80 diastolic. There were a few bronchial wheezes throughout the chest. The heart was not enlarged. The

*Lead IV, the chest lead, was taken in all the cases of the present series with exploring electrode at the cardiac apex, indifferent electrode on the left leg, and polarity so arranged that electrical negativity is represented by upward deflections and positivity by downward deflections.

TABLE

CASE NO.	DATE OF ADMISSION	AGE	SEX	ALCOHOL	CONDITION WHEN FOUND	ARTIFICIAL RESP.	CO_2-O_2 INHALATION	CONDITION ON ADMISSION
1	1/17/37	30	M	Yes	Unconscious	20 min.	1 hr. 15 min.	Semicomatose, responding to pain
2	1/18/37	23	M	No	Unconscious	None	1 hr. 8 min.	Comatose
3	1/25/37	54?	M	Yes	Unconscious	None	40 min.	Confused and disoriented
4	1/26/37	65?	M	Yes	Unconscious	None	2 hr.	Comatose
5	2/ 2/37	38	M	Yes	Unconscious	None	1 hr. 15 min.	Comatose
6	2/17/37	45	M	No	Unconscious	10 min.	40 min.	Stuporous
7	2/21/27	65	M	Yes	Unconscious	8 min.	47 min.	Irrational
8	2/21/37	68	M	Yes	Unconscious	8 min.	47 min.	Irrational
9	2/26/37	75	M	No	Unconscious	None	38 min.	Semicomatose
10	2/27/37	70	M	No	Unconscious	12 min.	43 min.	Stuporous
11	3/ 1/37	52	M	No	Unconscious	None	1 hr. 5 min.	Semicomatose
12	3/ 3/37	59	M	Yes	Unconscious	6 min.	1 hr. 18 min.	Semicomatose
13	3/ 3/37	82	M	No	Semiconscious	None	30 min.	Conscious negativistic
14	3/ 8/37	73	M	No	Unconscious	None	33 min.	Conscious
15	3/21/37	79	F	No	Unconscious	25 min.	40 min.	Stuporous
16	3/30/37	72	M	Yes	Unconscious	20 min.	66 min.	Stuporous
17	3/30/37	40	M	No	Unconscious	None	35 min.	Dull and drowsy
18	3/31/37	40	M	Yes	Unconscious	24 min.	2 hr. 27 min.	Comatose
19	4/ 9/37	56	F	No	Unconscious	10 min.	18 min.	Disoriented
20	4/10/37	54	M	Yes	Unconscious	None	45 min.	Drowsy and confused
21	4/21/37	57	M	No	Unconscious	10 min.	1 hr.	Drowsy
22	4/22/37	25	M	No	Unconscious	None	40 min.	Stuporous

PROBABLE DURATION OF UNCONSCIOUSNESS	ON ADMISSION			HEART EXAMINATION	DEGREE OF ARTERIOSCLEROSIS	RESULT
	TEMP. (° F.)	PULSE	BLOOD PRESSURE			
2 hr.	98.0	100	130/80	Normal.	0	Home on 3rd day.
12+ hr.	102.8	136	140/90	Normal.	0	Home after 7 days.
40 min.	101.8	110	130/90	Normal in size. Sounds distant.	++	Home on 14th day.
45 hr. (Died without regaining consciousness)	97.0	90	110/60	Normal in size. Sounds distant and of poor quality.	+++	Died on 3rd day.
3 hr.	98.6	132	90/65	Normal	0	Home on 4th day.
1+ hr.	94.6	96	150/90	Normal in size. Auricular fibrillation. Sounds of poor quality. No murmurs.	+	Home after 2 wk. in custody of brother. (Incompetent to take care of himself.)
1+ hr.	96.0	124	120/80	Normal in size. Sounds of fair quality. S_2 hollow. Short systolic blow at apex.	++	Home on 2nd day.
1+ hr.	95.4	116	105/60	Normal in size. Sounds distant. No murmurs.	+++	Home on 2nd day.
1+ hr.	98.2	128	100/60	Normal in size. Sounds of fair quality. No murmurs.	+++	Home on 2nd day.
3+ hr.	95.0	128	160/95	Normal in size. Sounds of poor quality. No murmurs.	+++	Died suddenly on 6th day.
5 hr.	96.4	120	110/70	Normal.	0	Home on 2nd day.
1½ hr.	96.0	110	108/76	Normal in size. Sounds of fair quality. Localized systolic blow at apex.	++	Home on 8th day.
30 min. (Semiconscious)	98.4	108	120/80	Sounds of poor quality. No murmurs.	++++	Home on 3rd day.
40 min.	95.4	120	132/66	Sounds loud and ringing. Systolic blow at apex. Size? (emphysema)	++++	Home on 2nd day.
1 hr.	96.6	76	170/64	Sounds loud, of poor quality. Short, rough systolic murmur at apex.	+++	Home on 4th day.
1½ hr.	97.0	86	110/50	Normal in size. Sounds loud. Systolic blow at apex.	+++	Observation in psychopathic division.
50 min.	97.8	128	130/100	Normal.	0	Home on 5th day.
11 hr.	95.0	114	100/60	Normal in size. Sounds of fair quality. No murmurs.	+	Home on 3rd day.
40 min.	95.0	116	140/70	Enlarged to left, 15 cm. in sixth intercostal space. Sounds of fair quality. No murmurs.	+++	Home on 2nd day,
45 min.	96.0	120	90/60	Normal.	+	Home on 3rd day.
2 hr.	98.0	58	128/80	Normal.	+++	Home on same day.
1 hr. 15 min.	97.6	114	88/65	Normal.	0	Home on 8th day.

TABLE II

CASE NO.	DATE	TIME AFTER ADMISSION	BLOOD PRESSURE	RATE	RHYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
1	1/17/37	15 min.	130/80	116	Regular	Normal	Normal	Normal	Rather level $S\text{-}T_4$	
	1/18/37	29 hr.	124/70	66	Regular	Normal	Normal	Normal		Late dip in Leads I, II, and III. Notch at end of T_4.
2	1/18/37	5 min.	140/90	130	Regular	Normal	Normal	Widened S in Leads I, II, and III.	$S\text{-}T_4$ convex, elevated, and high.	T_1 slightly diphasic. Low origin of T_2 and T_3.
	1/18/37	7 hr.	135/80	120	Regular	Normal	Normal	S-wave less wide.	$S\text{-}T_4$ high in origin but no longer upright.	T_1 now upright.
	1/19/37	27 hr.	110/75	About 90	Sinus arrhythmia	Normal	Normal	S-waves still a little prominent in Leads II and III.		Fairly normal in all leads.
	1/20/37	52 hr.	110/70	70	Sinus arrhythmia	Normal	Normal	Same	Same	Same
	1/23/37	5 days	114/70	72	Regular	Normal	Normal	S_2 and S_3 within limits of normal variation.	Normal	Essentially normal.
3	1/25/37	2 hr. 35 min.	130/90	100	Regular	Rather low in all leads	Normal	S_4 is down, as well as Q and R.	Normal	T_1 flat, T_4 upright.
	1/26/37	18 hr.	130/86	95	Regular	More normal	Normal	Normal	Normal	Unchanged
	1/27/37	44 hr.	140/90	74	Regular	As on first day	Normal	Normal	Normal	T_1 low, slightly upright, T_4 shallow.
	2/ 4/37	10 days	130/80	66	Regular	P_2 flat, P_3 inverted	Normal	Normal	Normal	T_1 inverted, T_2 very low with late slight rise, T_4 upright.

TABLE II—CONT'D

4	1/26/37	30 min.	110/60	88	VPC, left	Normal	Normal	Tendency to low voltage. Lead I = +5 Lead II = +4 Lead III = -1	Normal	T_1 rather low, T_4 shallow.
	1/27/37	27 hr.	134/70	130	Regular	Normal	Normal	Same	Normal	Same
5	2/ 2/37	20 min.	90/65	130	Regular	Normal	Normal	Normal	Normal	T_1 low (0.5 mm.).
	2/ 3/37	29 hr.	130/80	89	Regular	Normal	Normal	Normal	Normal	T_1 slightly higher (1 mm.).
6	2/17/37	5 hr.	150/90	AR 340 VR 90	A.F. (coarse)	--------	--------	S wide in all leads. S_4 upright	Normal	T_1 upright, T_2 low, T_3 inverted.
	2/18/37	26 hr.	145/90	VR 78-88	A.F. (less coarse)	--------	--------	Same	Normal	Same
	2/19/37	52 hr.	145/80	AR 390 VR 80	A.F.	--------	--------	Same	Normal	T_3 and T_4 shallower.
	2/20/37	3 days	140/84	VR 80	A.F.	--------	--------	Same	Normal	T_4 deeper again.
	2/23/37	6 days	138/80	VR 64	A.F.	--------	--------	Same	Normal	T_4 flat.
	3/ 1/37	12 days	140/80	VR 50	A.F.	--------	--------	Same	Normal	T_4 very shallow.
7	2/21/37	15 min.	120/80	VR 155	A.F.	--------	--------	Normal	Depressed in Leads I, II, and III. S-T_4 elevated.	T_4 upright.
	3/25/37	32 days	160/85	75	Regular	Normal	Normal	Normal	Normal	Normal
8	2/21/37	35 min.	105/60	VR 125	A.F.	--------	--------	Tendency to low voltage. Lead I = +2, -5 Lead II = +4, -1 Lead III = +1 to 2, -1 to 2	S-T_4 upcurved with high origin. S-T_2 slightly sagging.	T_1 low.
	3/25/37	32 days	150/75	75	Regular	Normal	Normal	Voltage normal	Normal	T_4 shallow.
9	2/26/37	20 min.	100/60	130	APC	--------	--------	Normal	S-T_4 somewhat convex	T_1 rather low.
	2/26/37	1¾ hr.	110/65	110	Regular	Normal	Normal	Normal	Normal	Normal
	5/ 3/37	66 days	160/90	94	Regular	Normal	Normal	Normal	Normal	T_3 inverted.

TABLE II—CONT'D

CASE NO.	DATE	TIME AFTER ADMISSION	BLOOD PRESSURE	RATE	RHYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
10	2/27/37	20 min.	160/95	130	Regular	P_2 and P_3 rather high	Normal	Tendency towards low voltage	Normal	T_2 high, T_1 low.
	2/28/37	24 hr.	120/85	134	Regular	Same	Normal	Same	Normal	T_1 flat, T_4 shallow.
	3/ 1/37	52 hr.	145/90	100	Regular	Lower	Normal	Little change	Normal	T_1 low, but slightly higher than on preceding tracing; T_4 more shallow; T_2 low.
11	3/ 1/37	45 min.	110/70	115	Regular	Normal	Normal	Normal	Normal	T_1 slightly low.
	5/14/37	74 days	145/90	78	Regular	Normal	Normal	Normal	Normal	Normal
12	3/ 3/37	35 min.	108/76	VR 130	A.F.	--------	--------	Normal	Normal	T_1 very low.
	3/ 4/37	29 hr.	140/90	100	Regular	Normal	0.2 sec.	Voltage lower	Normal	
	3/ 5/37	51 hr.	110/75	70	Regular	Normal	0.16 sec.	QRS_3 higher	Normal	T_3 normal.
	3/10/37	7 days	120/65	78	Regular	Normal	0.16 to 0.18 sec.	Same	Normal	Normal
13	3/ 3/37	15 min.	120/80	122	Regular	Normal	Normal	Widened and notched in all leads, low voltage.	Depressed in Leads I and II.	Diphasic T_1 and T_2. T_3 low.
	3/ 4/37	26 hr.	130/84	85	Regular	Normal	Normal	Same except for higher voltage.	Same	Same
14	3/ 8/37	20 min.	132/66	130	A.F.	Normal	--------	Low voltage, Leads I, II, and III. Lead I = +4 Lead II = +3, -1 Lead III = -2	$S\text{-}T_1$ and $S\text{-}T_2$ sagging. $S\text{-}T_4$ convex, with high origin.	Very low
	4/19/37	42 days	180/90	70	Regular	Normal	Normal	Improved voltage. Lead I = +7 Lead II = +3, -2 Lead III = -5	Normal	Normal

TABLE II—CONT'D

15	3/21/37	15 min.	170/64	72	Disturbance of auricular rhythm with variation in site of pacemaker.	Occasionally blocked. Sometimes inverted, upright, or isoelectric.	Varies from 0.2 to 0.45 sec.	Slurred in Leads II and III.	Very low origin of S-T_4.	T_2 and T_3 inverted.
	3/22/37	24 hr.	174/70	65 to 70	Variation in site of pacemaker continuous.	Changes less marked than on preceding day.	Same	Same	S-T_1 slightly depressed. Low origin of S-T_4 continues.	T_2 and T_3 inverted.
	3/24/37	3 days	175/75	65 to 75	Disturbance of auricular rhythm decreasing.	Fairly uniform in shape. Occasional blocked p-waves.	As long as 0.4 sec. at times.	Same	Changes less marked.	T_1 slightly upright. T_2 and T_3 inverted. Slightly low origin of T_4.
16	3/30/37	35 min.	110/50	About 90	Many VPC.	Normal	Normal	Normal	Normal	Low in Leads I, II, and III.
	3/30/37	7 hr.	110/60	100	Regular	Normal	Normal	Normal	Normal	T_1 upright. Higher in all leads.
	4/ 3/37	4 days	135/70	82	Regular	Normal	Normal	Normal	Normal	Same
	5/ 8/37	39 days	165/90	78	Regular with rare VPC.	Normal	Normal	Normal	Normal	Same
17	3/30/37	1 hr. 15 min.	130/100	135	Regular	Normal	Normal	Slightly low voltage. Lead I = +4 Lead II = +3, -2 Lead III = +2, -6	Normal	Normal
	3/31/37	23 hr.	120/95	95	Regular	Normal	Normal	Normal voltage	Normal	Slight late inversion of T_1; T_2 very low; T_3 very shallow.
	4/ 3/37	4 days	125/85	104	Regular	Normal	Normal	Same	Normal	Low upright T_1; T_2 higher; T_3 slightly inverted; T_4 shallow.

TABLE II—CONT'D

CASE NO.	DATE	TIME AFTER ADMISSION	BLOOD PRESSURE	RATE	RHYTHM	P-WAVES	PR	QRS	S-T	T-WAVE
18	3/31/37	1 hr.	100/60	120	Regular	Normal	Normal	Normal	S-T_4 rather level.	T_1 low.
	4/ 1/37	18 hr.	108/80	80	Regular	Normal	Normal	Normal	S-T_4 more normal.	T_1 low; slight dip at end of T_2 and T_3; late rise in T_4.
19	4/ 9/37	15 min.	140/70	104	Regular	Normal	0.19 sec.	Marked L.A.D.	Normal	T_1 diphasic; T_4 upright.
	5/29/37	50 days	180/88	75	Regular	Normal	Normal	Same	Normal	T_1 diphasic; T_2 and T_3 inverted; T_4 diphasic.
20	4/10/37	1 hr.	90/60	105	Regular	Normal	Normal	Normal	Normal	T_1 and T_2 low.
	4/10/37	5 hr.	130/90	102	Regular	Normal	Normal	Normal	Normal	T_1 and T_2 higher.
	4/11/37	28 hr.	130/85	74	Regular	Normal	Normal	Normal	Normal	Normal
21	4/21/37	45 min.	120/80	55	Regular	Normal	Normal	Normal	Normal	Normal
22	4/22/37	25 min.	88/65	110	Regular	Normal	Normal	Normal	Normal	T_1 low; T_4 slightly shallow.
	4/23/37	24 hr.	100/70	64	Sinus arrhythmia	Normal	Normal	Normal	Normal	T_1 very low; T_4 slightly shallow.
	4/24/37	48 hr.	105/70	58	Sinus arrhythmia	Normal	Normal	Normal	Normal	T_1 low; T_4 more shallow.
	4/27/37	5 days	100/65	55	Sinus arrhythmia	Normal	0.19 sec.	Normal	Normal	T_1 slightly higher; T_4 shallow.
	4/29/37	7 days	106/70	50	Sinus arrhythmia	Normal	Normal	Normal	Normal	Normal

heart sounds were of poor quality. The rate was rapid and apparently regular. The liver was not enlarged; there were no râles at the lung bases and no peripheral edema. The peripheral vessels were moderately sclerotic.

An electrocardiogram was taken thirty minutes after the patient was admitted and showed auricular fibrillation with a heart rate of 155 per minute, depressed S-T segments in Leads I, II, and III, and an elevated S-T segment in Lead IV. The T-wave in Lead IV was upright.

Within three hours after admission the patient became less noisy and talked coherently. He left the hospital against advice early the next morning.

This patient was followed up one month later. At that time he denied noticing any ill effects from the gas poisoning. On examination his chest was clear, and the heart sounds were of better quality. His blood pressure was 160 systolic, 85 diastolic. An electrocardiogram taken at this time was essentially normal, the rhythm being regular at 75 per minute and the changes in the S-T segments and T-waves noted in the previous electrocardiogram being absent.

CASE 4.—This patient, an elderly white male, was found unconscious in his room which was filled with gas escaping from a leaking fixture. After being treated with carbon dioxide and oxygen inhalations for two hours he was brought to the hospital, still unconscious.

On admission the patient was in profound coma, with deep stertorous respiration, slight cyanosis of the lips, and cold extremities. The temperature was 97° F., the pulse 96, and the blood pressure 110 systolic and 60 diastolic. The lungs were clear except for a few wheezes. On percussion the heart was apparently normal in size. The sounds were distant and regular except for occasional extrasystoles. The liver was not enlarged, and there was no edema. Peripheral arteries were very sclerotic. Tendon reflexes were hyperactive, but there were no abnormal responses.

An electrocardiogram taken thirty minutes after admission showed ventricular premature contractions (left), with right axis deviation. The rate was 88 per minute. The QRS complexes showed a tendency to low voltage. T-wave changes were rather low T_1 and shallow T_4.

The next day the patient was still in coma. The temperature was 103.8° F., the respiration 48, and the blood pressure 134 systolic and 70 diastolic. Heart sounds were louder than on admission but of poor quality. There were many moist râles at both lung bases. The liver was not enlarged, and there was no edema. The white blood count at this time was 21,000, with 91 per cent polymorphonuclear leucocytes.

A second electrocardiogram was taken twenty-seven hours after admission. The rhythm had become regular, but the rate had increased to 130 per minute. The QRS complexes were of low voltage, as in the first electrocardiogram. No new changes had appeared.

The patient's temperature continued to rise and the moist râles at the lung bases increased. He died forty-two hours after admission without regaining consciousness. No autopsy was performed.

RESULTS

In our series of twenty-two cases of carbon monoxide asphyxia, the most common electrocardiographic deviation is an abnormality in the T-waves or in the level of the S-T segment, there being 18 such cases (Cases 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 20, and 22). Four cases (Cases 7, 8, 12, and 14) showed paroxysmal auricular fibrillation, and one (Case 2) showed transitory intraventricular block. Two (Cases 4 and 16) showed ventricular premature contractions, and one

(Case 9) auricular premature contractions. Low voltage on the initial electrocardiogram, later improving or returning to normal, was present in five cases (Cases 4, 8, 13, 14, and 17). Variations in the P-waves occurred in two (Cases 3 and 10).

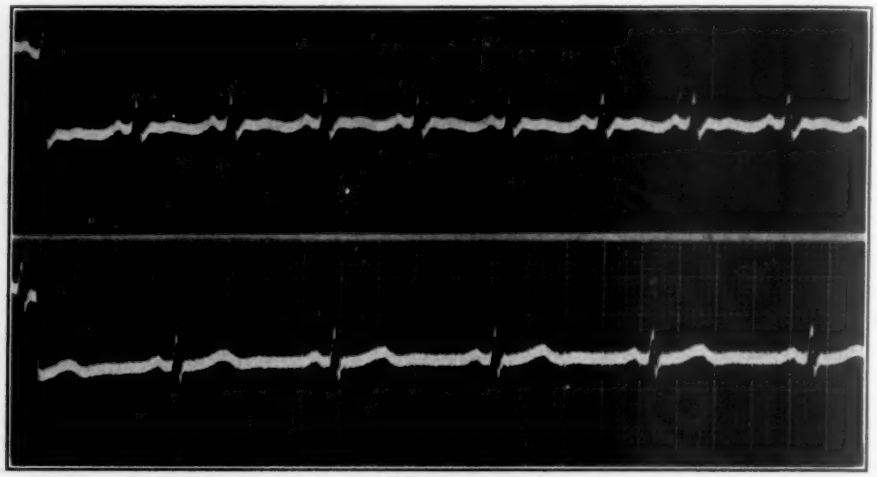

Fig. 1.—*A*, Lead I from Case 2 on admission to the hospital, showing low diphasic T-waves. *B*, Lead I from Case 2, five days later, normal.

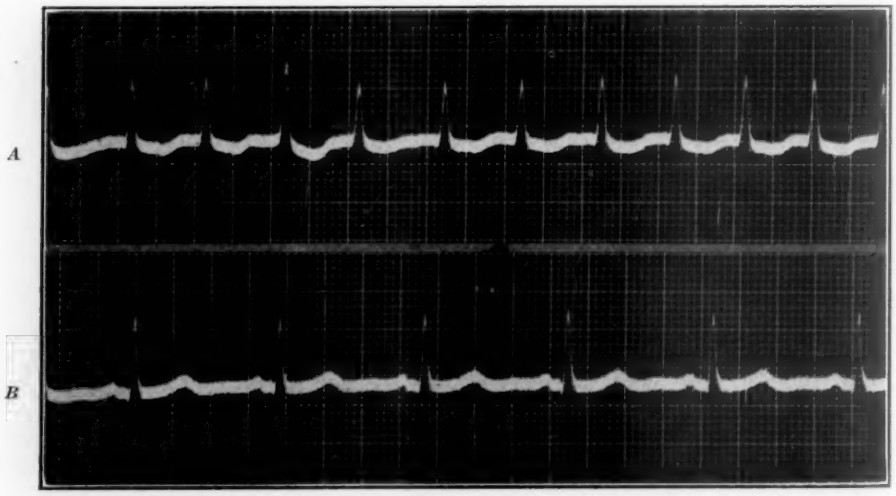

Fig. 2.—*A*, Lead I from Case 7 on admission to the hospital, showing auricular fibrillation and depressed T-waves. *B*, Lead I from Case 7, thirty-two days later, normal.

We feel that the above changes, having been transitory, may be ascribed directly to the carbon monoxide asphyxia, except when coronary disease may have paved the way in some cases. However, the importance that can be attached to the poisoning in several other cases is less clear-cut. In Case 15 there was a marked disturbance of auricular rhythm,

with variation in the site of the pacemaker. This had decreased three days after admission when the last electrocardiogram was taken and when the patient was lost for further study, but, lacking a follow-up, the most that can be said is that the asphyxia probably aggravated a condition already present in a seventy-nine-year-old woman who had arteriosclerosis and hypertension.

In regard to Case 6, doubt again exists as to the rôle played by the asphyxiation. This forty-five-year-old man gave no history of any symptoms suggestive of preexisting heart disease, and examination yielded no clue as to an etiology for such disease. Yet, upon his admission to the hospital, auricular fibrillation was found to be present. Electrocardiograms taken through the twelfth day of his two-week stay in the hospital all showed auricular fibrillation and intraventricular block. The evidence is far from conclusive that the changes found in this patient were solely the result of his carbon monoxide poisoning. It is more probable that he had preexisting auricular fibrillation and intraventricular block on a basis of coronary disease.

In Case 13 no definite conclusions can be drawn as to the etiology of the intraventricular block which was present, this patient being 82 years of age, markedly arteriosclerotic, and providing no follow-up after the second day. It is quite possible that coronary disease and gas poisoning each played a rôle.

DISCUSSION

We have found one report of a patient overcome by carbon monoxide who was followed with frequent electrocardiograms (Colvin,[1] 1927). A young man seriously poisoned by gasoline exhaust was completely comatose on admission to the hospital and was given inhalation treatment. Approximately seven hours after admission the patient could be roused, but he was mentally dull for three days. An electrocardiogram taken twenty-four hours after the poisoning occurred showed intraventricular block; a second electrocardiogram taken three days after the poisoning showed improvement but still indicated impaired conduction in the ventricles. By the sixteenth day all abnormal changes had disappeared, and the patient was considered perfectly sound.

As noted already our findings are limited to the period of recovery from the marked anoxemia after emergency oxygen and carbon dioxide treatment. How much more extensive and uniform the electrocardiographic changes might have been at the height of the poisoning, we have no knowledge; it seems likely that they would have been greater than at the stage of our examination. So far as they go, our results, while indicating that intraventricular block may result from carbon monoxide poisoning, suggest that such is not the usual finding. Case 2 is the only one which can be said to show this type of conduction disturbance as an aftermath of asphyxia. Furthermore, this patient, who was uncon-

scious for over twelve hours, showed only the merest trace of intraventricular block twenty-seven hours after admission. Five days after admission his electrocardiogram was essentially normal. Whether or not the fact that the patient reported by Colvin was overcome by gasoline exhaust, whereas our patient was overcome by illuminating gas, accounts for the much more prolonged conduction disturbance in the former case is problematical.

In general our results tend to agree with those obtained by Haggard[2] (1921) in his work with dogs. Gassing dogs to death rapidly (twenty-five to forty minutes) with a high concentration of gas, and more slowly (five to seven hours), using lower concentration of carbon monoxide, and taking electrocardiograms at intervals, he found that "no evidence of impairment of cardiac conduction developed until respiration had failed." When an extreme degree of asphyxia was present, the most characteristic change was heart-block. As pointed out earlier, none of our patients was seen at the stage of such profound asphyxia. However, Haggard gassed three dogs to the stage at which artificial respiration was necessary to bring about their recovery. Electrocardiograms for the first four hours showed tachycardia with T-waves in the direction opposite to normal. Electrocardiograms taken after twenty-four hours showed normal rate and T-waves. Similarly, two out of three animals gassed into the stage of complete respiratory failure, with the development of partial heart-block as shown by electrocardiogram, were revived with 8 to 10 per cent carbon dioxide in oxygen inhalations. A few minutes after the cessation of the inhalation treatment all evidence of impaired conduction had disappeared. Although the preceding experiments were carried out using a mixture of pure carbon monoxide and air, Haggard found that the results were essentially the same when an illuminating gas and air mixture was used.

The changes in the T-waves and in the S-T segments which some of our cases demonstrated are somewhat similar to those reported by Katz, Hamburger, and Schutz[3] (1934) in experimentally produced generalized anoxemia. Their subjects rebreathed air from which the carbon dioxide was removed, and electrocardiograms were taken at stages of extreme oxygen deprivation. The "most consistent changes in the electrocardiogram were a flattening of the T-wave in one or more leads, in some instances followed by its inversion. . . . In practically every instance, the level of the S-T segment tended to be shifted downward during anoxemia," the maximum effect being observed when the oxygen content was lowest, and the changes tending to disappear rapidly upon resumption of breathing room air.

CONCLUSIONS

1. Carbon monoxide asphyxia, even though severe enough to cause death, may produce no important electrocardiographic changes.

2. Changes in the T-waves and in the S-T segments occur most frequently.

3. Paroxysmal auricular fibrillation may occur, as a rule in patients within the age group in which any physiologic insult or trauma may cause this condition.

4. One case of transitory intraventricular block is present in the series.

5. No cases of auriculoventricular block definitely attributable to carbon monoxide poisoning were found, although one case is reported in which a marked disturbance of auricular rhythm with partial auriculoventricular block was apparently aggravated by the asphyxia.

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THE BLOOD PRESSURE AND THE SIZE OF A CARDIAC INFARCT*

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DURING the course of studies on the action of certain drugs in cardiac infarction in the cat,[1, 2] there occurred an opportunity to make observations on the level of the systemic blood pressure three weeks after ligation of a coronary artery and on the relation of the blood pressure to the size of an infarct, the area of which was accurately measured. So far as we know, this subject has received little attention in survival experiments after production of a cardiac infarct. Several of the more important studies are listed.[3]

The blood pressure was determined in 27 cats three weeks after ligation of a large coronary artery (the left circumflex at its origin in all instances but one); in 12 control animals three weeks after the main branches of the left coronary artery had been similarly exposed but not ligated; and as further control, in a group of nine normal (unoperated upon) animals. At this time, when examined by the "blind test," the control animals were as a rule indistinguishable from those in which infarction was present. Mean blood pressure was recorded by a mercury manometer, by means of a cannula inserted in the carotid artery under local anesthesia. Several readings were taken when the animal was quiet, and the average of these was calculated. This average will be referred to as the mean blood pressure.

Approximately one-half the animals with infarction were treated with aminophylline during the three weeks after operation, but, since the behavior of the blood pressure in this group was essentially the same as in that not treated with this drug, all the animals with infarction are presented in this study as a single group. Details of the treatment by aminophylline, the operative techniques, and the measurement of the infarct by means of the planimeter have been described,[1] and the blood pressure figures in the individual experiments are included in another report.[2]

The results are summarized in Table I. The average mean blood pressure was essentially the same for all groups of animals: after cardiac infarction 150 mm., after the control operation 155 mm., and in the unoperated controls 152 mm., the average for all controls being 154 mm. The range in mean blood pressure for the individual experiments was also similar in the control (120 to 185 mm.), and in the infarcted (120

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to 183 mm.) groups. Under the conditions of these experiments, therefore, the level of the blood pressure was normal three weeks after acute infarction.

The data were analyzed to ascertain whether an animal with a large infarct was more likely to have a low blood pressure than one with a small infarct. Plotting mean blood pressure against infarct size failed to reveal a correlation between these two variables (Fig. 1). Furthermore, it was found (Table I) that when the animals having the small-

TABLE I

ANALYSIS OF THE BLOOD PRESSURE IN RELATION TO INFARCT SIZE

GROUP	NUMBER OF ANIMALS	MEAN BLOOD PRESSURE MM. HG	SIZE OF INFARCT SQ. CM.	DIFFERENCE ABOVE OR BELOW MEAN PRESSURE OF CONTROLS PER CENT
Control Animals	21	154	none	0.0
Infarcted Animals	27	150	5.55	−2.6
		Infarcted Animals		
Smallest infarcts	13	153	3.60	−0.6
Largest infarcts	14	147	7.36	−4.5
Smallest infarcts	5	151	2.92	−1.3
Largest infarcts	5	144	9.29	−6.5
Highest mean pressures	13	162	5.10	+5.2
Lowest mean pressures	14	139	5.96	−9.7
Highest mean pressures	5	172	4.51	+11.7
Lowest mean pressures	5	129	6.61	−16.2
		Control Animals		
Highest mean pressures	10	167	none	+8.5
Lowest mean pressures	11	141	none	−8.5
Highest mean pressures	5	176	none	+14.3
Lowest mean pressures	5	133	none	−13.6

est infarcts and those having the largest infarcts were grouped separately, the average mean pressure did not deviate more than 6.5 per cent from the normal in either case, although the average infarct size in one group was more than three times as large as that in another. When those groups having the highest and lowest pressures were examined separately, it was found that those having the lowest pressures also had on the average somewhat the larger infarct. That this might be purely accidental, however, was suggested by the finding that these low pressures were not appreciably lower than those among a similar small number of normal animals, similarly selected.

That the blood pressure was normal three weeks after coronary occlusion and that this was so in the case of both very large and very small infarcts were unexpected results. They are in contrast to those which prevail in clinical coronary thrombosis, as in a high proportion of these cases the blood pressure does not return to its previous level.[4] The reasons for these differences between the cat and the human are not

clear, but, in attempting to explain them, consideration should be given to possible differences in the reflex compensatory mechanisms for maintaining blood pressure in the two species, to differences in the location of the infarct, for the artery most frequently occluded in man is the anterior descending branch of the left coronary rather than the left circumflex,[4, 5] and to the fact that in the cat, except for the infarct, the heart and blood vessels are normal, whereas in man infarction is usually associated with additional pathologic changes in the cardiovascular system. It is conceivable that the nature or extent of these latter changes may be partially disclosed by the behavior of the blood pressure after infarction, and some light, therefore, may be thrown on prognosis. Levine and Brown[4] state that in coronary thrombosis it is their "general impression that the patients who have done the best were those who

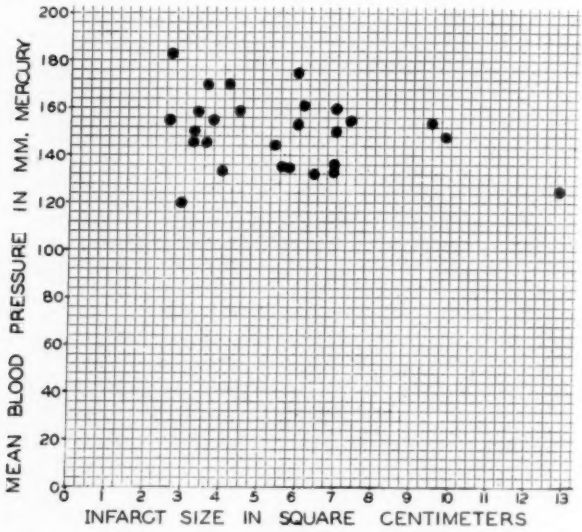

Fig. 1.—Mean blood pressure is plotted against infarct size. Note the wide scatter of the points, and lack of correlation between the two.

showed a marked fall with only a slight increase in the blood pressure." The majority of clinical surveys on the course and prognosis of this disease,[6] except in regard to its association with hypertension, pay scant attention to the significance of changes in the systemic blood pressure subsequent to the acute attack. We have not determined the complete course of the blood pressure changes after infarction, inasmuch as the operation for experimental coronary occlusion introduces serious technical difficulties. Our results, as far as they go, however, indicate that the fairly rapid restoration of the normal blood pressure is likely to prove misleading if used as a basis for an inference regarding the size of the infarct. They should serve to focus attention on the need for systematic correlations between the blood pressure curve, post-mortem findings and prognosis in clinical coronary thrombosis.

SUMMARY

In the cat with an otherwise normal circulation, the blood pressure is almost invariably normal three weeks after the ligation of a large coronary artery (left circumflex). This applies to infarcts of widely different sizes, ranging from a relatively small area involving the upper third of the left ventricle posteriorly to a very large one including nearly all of the left ventricle posteriorly, together with adjacent strips of the right ventricle and interventricular septum.

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THE CORONARY VASOCONSTRICTOR ACTION OF FOREIGN SPECIES BLOOD*†

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DURING the course of preliminary studies in developing a method for perfusion of the coronary arteries in the beating heart of the dog, tests were run using freshly defibrinated blood of the sheep, beef, and pig (obtained from the slaughter house through the courtesy of Dr. D. Klein, of Wilson Laboratories) as a perfusate. It was soon apparent that this foreign species blood was incompatible with the isolated beating heart when employed in the same manner as dog blood (Katz, Jochim, and Bohning[1]), and, after a number of attempts to make this foreign blood suitable, its use was discontinued. Evidence was obtained in the course of these experiments that the incompatibility of the foreign species blood for our purpose was due largely to the persistence of a coronary vasoconstrictor action. We consider this coronary vasoconstriction by foreign blood of sufficient importance to merit the presentation of our findings.

EXPERIMENTAL DATA

We first tested the effect of the foreign species blood on the blood pressure when injected repeatedly into normal dogs anesthetized with nembutal. During each injection, an equal amount of the dog's own blood was removed to keep the blood volume constant.

For the first experiment the defibrinated beef blood was filtered six times through a fine meshed cloth in preparation for injection into the animal. The first substitution of 100 c.c. of beef blood caused a profound drop in mean blood pressure after a short lag, and it required about 15 minutes for the blood pressure to return to normal. After two such substitutions, a 50 c.c. substitution had practically no effect, but a 200 c.c. substitution, which was tried next, caused so profound and sustained a pressure drop that the animal died. On postmortem examination marked pulmonary edema was found.

In the second dog the first substitution of 100 c.c. of blood also caused a delayed, profound and prolonged depressor effect, but this was preceded by a definite pressor effect. This was the only experiment in the course of this work in which such a preliminary pressor action was noted. Repetition of this substitution, which was done twenty-nine times, resulted in a progressive diminution and ultimate

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†Aided by the Emil and Fanny Wedeles Fund for Cardiac Research.

abolition of the depressor response without any apparent effect on the preliminary pressor response. This animal was in good condition when killed one and one-half hours after the first beef blood substitution.

In the third dog, segments of whose blood pressure curve are shown in Fig. 1, the filtered beef blood was passed through the lungs of a dead dog to see if this would abolish the depressor effect. It was found that the first substitution still caused a delayed, profound, and prolonged depressor effect. Repetition of this substitution carried out twenty-five times led to the diminution and ultimate abolition of this depressor effect. The dog was in good condition when killed three and one-half hours after the start of the first substitution. A similar abolition of the depressor effect of beef blood was obtained in three other dogs.

These experiments indicated that the injection of slaughter house blood into the living animal causes a depressor action to which the

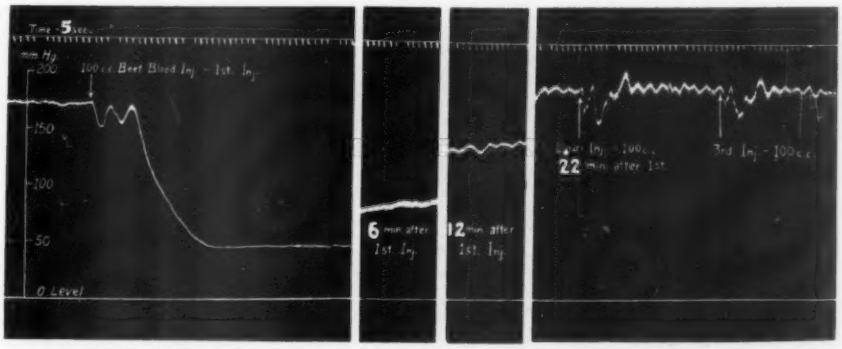

Fig. 1.—Blood pressure curve from an anesthetized dog to show the typical effect of repeated substitutions of 100 c.c. of beef blood for an equal amount of the dog's blood. The disappearance of the profound delayed depressor response seen in injections subsequent to the first is clearly visible. Discussed in text.

dog can be made refractory. Since similar depressor responses did not occur when we used hemoglobin solutions of beef blood, prepared according to the technique of Amberson and his co-workers,[2] the depressor response must have been due to a foreign element in the serum.

Following this experience, we made it a routine practice to make the recipient dog refractory to this depressor action before establishing the isolated beating heart preparation. In principle we followed the method employed in desensitizing patients susceptible to horse serum. Usually we began with an intravenous injection of 5 c.c. of a 1:5 dilution of beef blood in isotonic saline. Gradually increasing doses were given as the animal became more refractory until 5, 10, 50, and 100 c.c. of whole beef blood could be given without causing a depressor response. Our earlier experience showed that this refractory state lasted several hours —sufficient time in which to make and conduct experiments in the isolated heart preparation.

However, actual trial in the use of this foreign blood to perfuse the coronary circuit in the beating heart according to the technique employed previously with dog's blood[1] met with failure, even though the recipient dog had become refractory to the depressor action. Whenever used, the heart of the isolated preparation after developing premature systoles went into ventricular fibrillation, and this occurred at most within five minutes after the coronary arteries were cannulated, and often even before the cannulation was completed. In all instances except one, no measurable coronary flow could be obtained, although the coronary inflow pressure was anywhere between 100 and 150 mm. Hg. In the one instance, a flow of 60 c.c. per minute was obtained for a few minutes after the coronary cannulation was completed, but the flow soon stopped entirely. Autopsies showed that in these animals the coronary

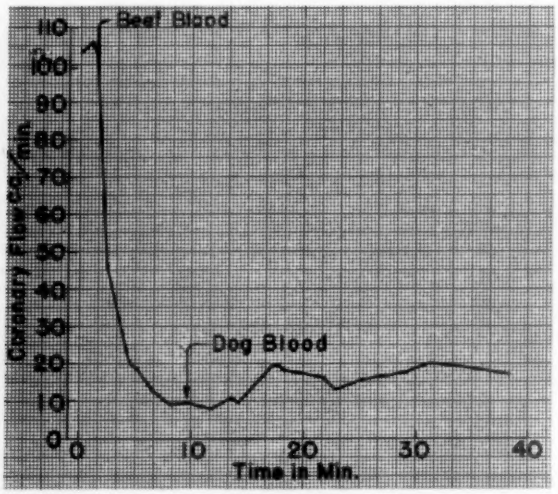

Fig. 2.—Coronary blood flow changes produced in an isolated fibrillating dog heart by substituting as a coronary perfusate beef blood, to the depressor action of which the dog had been made partially refractory. Discussed in text.

arterial and sinus cannulae were in place and not kinked and that the major superficial coronary arteries were patent.

This experience suggested that the deleterious action of beef blood on the isolated dog heart was due to a vasoconstrictor action of the beef blood on the coronary vessels. This conclusion was verified by actual test in an isolated fibrillating heart, the coronary vessels of which were perfused with beef blood after the dog had been made refractory to the depressor action of the beef blood. The preparation was first established with dog's blood as the perfusate in the manner previously described by us.[3] After the coronary flow had become stabilized, the beef blood, prepared in exactly the same way as the dog's blood,* was substituted as a perfusate, and after a few minutes again replaced

*The dog's blood used as a perfusate was obtained from several dogs as previously described.[1]

with dog's blood. The results on coronary flow are shown in Fig. 2. It will be seen that during the perfusion with beef blood a marked coronary vasoconstriction appeared, and the coronary flow decreased to 9 per cent of its previous level. This marked decrease in flow was only slightly relieved when the preparation was reperfused with dog's blood, the flow remaining at a level of 18 per cent of its original value. Histologic examinations of this heart by Dr. Otto Saphir, of the Department of Pathology, revealed no significant intravascular clotting. The absence of intravascular clotting and the tendency for the constriction to be reversed by dog's blood indicates that the serum of this foreign blood contains a vasopressor substance for the dog's coronary vessels.

The presence of this coronary vasopressor response in the perfused heart and its absence in the entire animal made refractory to the de-

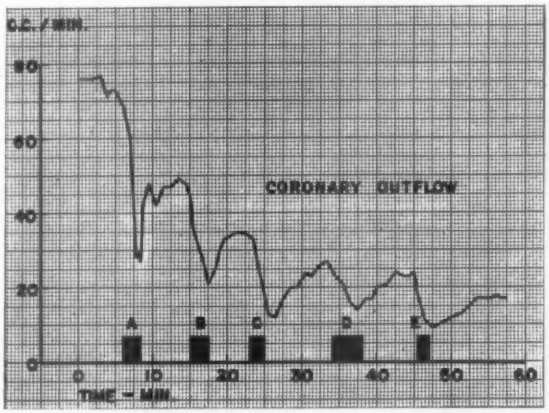

Fig. 3.—Coronary blood flow changes produced in an isolated fibrillating heart by the following bloods:

A, 100 c.c. of blood from a dog made refractory to the depressor action of beef blood (containing 10 per cent beef blood).

B, 120 c.c. of normal dog blood to which 5 per cent beef blood had been added.

C, 70 c.c. of the same blood as *A* except for the addition of 5 per cent more beef blood.

D, 95 c.c. of normal dog blood to which 20 per cent beef blood had been added.

E, 50 c.c. of whole beef blood. Discussed in text.

pressor action of beef blood might be due to (a) the greater concentration of beef blood reaching the heart in the former case, (b) the use of blood from dogs not made refractory to the depressor action of beef blood in the initial perfusion, or (c) the absence of a refractory state in the heart to the action of beef blood, the protection of the heart in the whole animal being the result of the action of other organs which are removed in making the isolated heart preparation. Two types of experiments were devised to test these possibilities. In the first, an isolated fibrillating heart preparation such as used in the preceding experiment[3] was made in a dog which had previously been made refractory to the depressor action of the beef blood. The dog's

blood for the perfusate was obtained from animals not previously exposed to beef blood. At varying intervals small quantities of the following bloods were substituted as a perfusate: (a) blood from a dog made refractory to the depressor action of beef blood; this contained roughly 10 per cent beef blood accumulated in the process of rendering the animal refractory; (b) a 5 per cent solution of beef blood in the dog's blood used in the original perfusion; (c) a 5 per cent solution of beef blood in the dog's blood used in (a), really making a 15 per cent beef blood solution; (d) a 20 per cent solution of beef blood in the dog blood used in the original perfusion; and (e) whole beef blood. All the bloods used were defibrinated and prepared in the usual manner. The foreign blood could be temporarily substituted as a perfusate under the same pressure and temperature as the original blood used for perfusion simply by turning a stopcock when desired. The results of this experiment are shown in Fig. 3. It will be seen that all five samples containing beef blood caused a reversible vasoconstriction of the coronary vessels, the constriction tending to be abolished when the original dog's blood perfusate was again used. This experiment shows that the presence of blood derived from an animal made refractory to the depressor action of the beef blood did not appreciably modify the vasoconstrictor action of beef blood.

The second type of experiment was to note the effect of substituting whole beef blood for dog's blood as a perfusate in an isolated fibrillating heart preparation taken from a dog rendered so refractory to beef blood that the animal's entire blood volume could be rapidly changed without a depressor action. Two such experiments were carried out. In both, the animals were made so refractory to the depressor action of beef blood that 1100 c.c. and 1700 c.c. of beef blood, respectively, could be substituted for the animal's own blood in a matter of four and one-half and fourteen minutes without causing any appreciable blood pressure drop. In both these animals the isolated perfused fibrillating hearts were found to be refractory to the coronary vasoconstrictor action of beef blood when this was substituted as a perfusate for dog's blood. These last experiments indicate convincingly that the heart can be rendered refractory to beef blood provided the process is carried far enough. The apparent absence of refractoriness in the earlier experiments indicates merely that the process of rendering the animal refractory had not been carried far enough.

DISCUSSION

These results strongly suggest that the depressor action of the foreign blood in the dog may be contributed to by a cardiogenic factor resulting from the coronary vasoconstriction demonstrated in this isolated organ. It may prove to be that the serious and often fatal result obtained in

anaphylactic shock is in part contributed to by such a coronary vasoconstrictor action in susceptible individuals. This is in accord with the recent observations of Wilcox and Andrus,[5] who demonstrated that coronary constriction occurred in an isolated guinea pig heart following the administration of the protein to which the animal had become sensitive. The evidence presented by Wilcox and Andrus that this coronary constriction is due to histamine is not in accord with observations made in this laboratory on the dog since we found that histamine causes coronary vasodilation.[3]

We have no evidence which could point to the nature of this coronary vasopressor substance; our previous results showing that acetylcholine is a coronary vasodilator[3] would exclude this substance. We are reporting these experiences with beef blood since they show coronary vasoconstriction to a degree which may truly be called spasm. Apparently, the substance giving rise to this action is in the serum of the foreign blood and would appear to be of the nature either of a foreign protein or of one of its breakdown products.

The possibility that the foreign blood coronary "spasm" might be in the nature of a specific foreign protein affair raises the question as to whether or not similar types of reactions may not follow in susceptible individuals when foreign proteins enter the blood stream. We cannot resist the temptation to speculate that this may on occasion lead to severe coronary vasoconstriction in man and help to explain some cases of acute coronary insufficiency and angina pectoris, especially if the coronary vessels are already the seat of narrowing in the larger channels. Vasoconstriction affecting the smaller arteries under these circumstances would increase the resistance to flow in the already narrowed coronary bed. At present, however, this must be regarded as a mere conjecture. Our results lend support to the long-established clinical concept of intense coronary "spasm" since such a state had been demonstrated by our experiments to actually occur in the experimental animal.

SUMMARY

A delayed, profound, and prolonged depressor action occurred when a small amount of beef blood (also sheep's and pig's blood) was injected into a normal anesthetized dog. This depressor response could be progressively lessened and finally abolished by repeated injections of beef blood gradually increased in amount, the dog's own blood being withdrawn in equal amounts. When, however, this dog's heart was completely isolated and its coronary arteries were perfused with the same beef blood, ventricular fibrillation rapidly ensued, and the coronary inflow markedly decreased and finally stopped, indicating an intense coronary "spasm." Evidence is presented suggesting that

this is a real coronary vasoconstriction, and that the substance responsible for this is made ineffective in the whole animal and in the isolated heart when the animal is made sufficiently refractory to the depressor action by repeated passage of the beef blood through the animal.

We are indebted to the other members of the department for technical assistance.

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OCCLUSION OF THE CORONARY ARTERIES BY HEMORRHAGE INTO THEIR WALLS*

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OCCLUSION of the coronary arteries may be the result of one of the following lesions or a combination of several of them: (1) thrombosis, (2) intramural coronary arterial hemorrhage, (3) severe arteriosclerosis with stenosis, (4) syphilitic aortitis and coronary arteritis with narrowing of the ostia, (5) endarteritis, and (6) embolism.

The commonest cause of occlusion is thrombosis of an artery which is the seat of severe partially occluding sclerosis. Intramural coronary arterial hemorrhage, which is probably the second most common cause, has received scant attention, and has never been considered as a cause of death. However, careful study shows that many coronary arteries are occluded not as the result of thrombosis but of massive hemorrhage into the vessel wall with the formation of a large hematoma which blocks the lumen either by virtue of its size or by rupture through the intima and subsequent development of a thrombus. The purpose of this report is to describe seven patients who died not as the result of thrombosis but of intrinsic intramural hemorrhage.

CASE REPORTS

CASE 5543.—A white man, 61 years of age, a restaurant proprietor, had noticed increasing dyspnea and fatigue upon exertion for ten months before admission to the hospital. He had been examined by a physician who sent him to bed and gave him digitalis. Nevertheless, his symptoms became worse, and he developed attacks of severe precordial pain which radiated down the left arm. The patient, as well as his mother and father, had diabetes mellitus.

The blood pressure was 140/80, the temperature 38° C., and the pulse 100. The heart was slightly enlarged, and the sounds were of poor quality, with a marked gallop rhythm and pulsus alternans. A soft blowing systolic murmur was heard over the aortic area and at the apex. There was marked cyanosis and dyspnea, with Cheyne-Stokes respiration. Congestive failure was severe. The white blood cell count was 8,600. The electrocardiogram showed notching of the QRS interval, with an abnormal S-T complex in Leads I and III. The P-R interval was 0.12 sec. This graph was interpreted as representing a combination of myocardial damage and digitalis effect. The patient's symptoms increased in severity, and he died four days after admission to the hospital and ten months after the onset of symptoms.

At autopsy the heart weighed 650 gm. There was both recent and remote infarction of the entire right ventricle, with mural thrombi in the right ventricle and auricle. The pericardial sac was obliterated by dense, fibrous adhesions.

*From the Institute of Pathology, Western Reserve University, and The University Hospitals.

Both coronary arteries showed severe sclerosis with narrowing of the lumen. The right coronary artery, at a point 5 cm. from the ostium, was occluded by soft, dark red blood clot. Serial sections through this portion showed intramural arterial

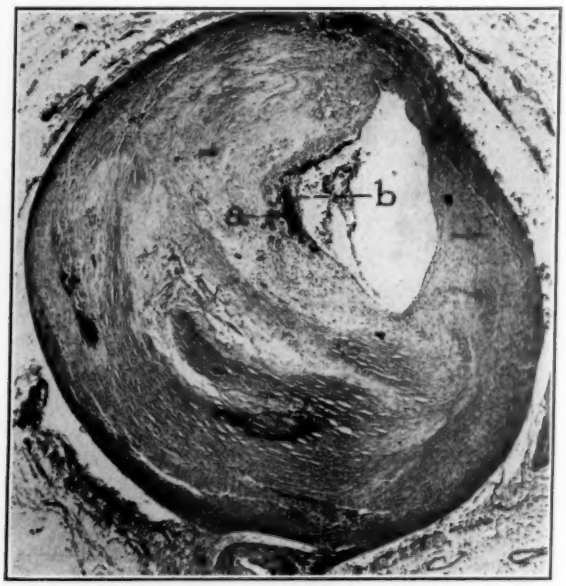

Fig. 1.—Case 5543. A section through the edge of the occluded portion of the right coronary artery, showing several recent hemorrhages, *a*, in the intima. The endothelial lining, *b*, is intact.

Fig. 2.—Case 5543. A section 1 mm. distal to Fig. 1. The hemorrhages, *a*, are covered by endothelium, *b*, but bulge into the lumen.

hemorrhage just beneath the intimal endothelium which at no point was ruptured (Figs. 1, 2, 3, and 4). There was no thrombosis, but the vessel was completely occluded by the large hematoma.

CASE 5561.—A white male, 43 years of age, a press operator, stated that ten days before admission to the hospital he was suddenly stricken with crushing sub-

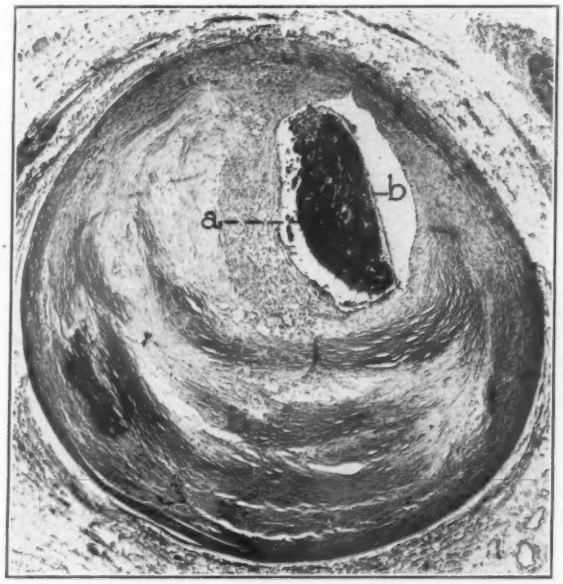

Fig. 3.—Case 5543. A section 4 mm. distal to Fig. 1. A large hematoma, *a*, is present, which has obstructed the lumen. The endothelial lining, *b*, is intact.

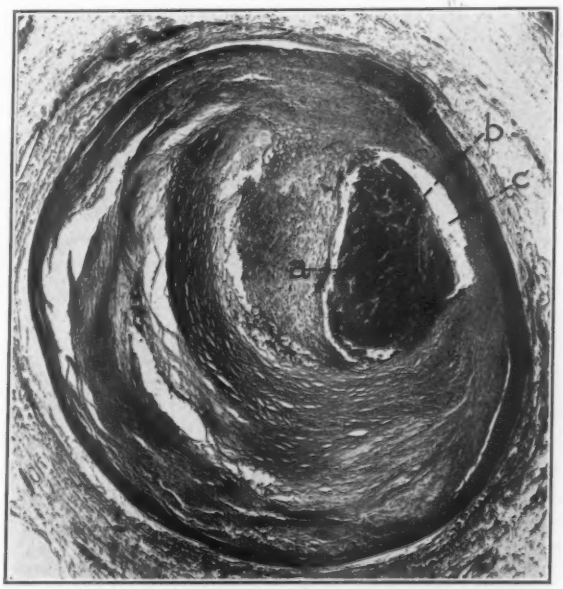

Fig. 4.—Case 5543. Occlusion of the lumen, *c*, by the subendothelial hematoma, *a*. A section 5 mm. distal to Fig. 1.

sternal pain which radiated to both shoulders and down the arms. The pain recurred at irregular intervals. His mother had died at 52 years of age of a cerebral hemorrhage.

The blood pressure was 118/88 but dropped to 85/55 shortly after admission to the hospital. The temperature was 37.5° C., the pulse 92, and the respirations 16. There was slight dyspnea. Although distant, the heart sounds were distinct, and a short time after admission a loud pericardial friction rub appeared. The white blood cell count was 14,650, with a preponderance of polymorphonuclear neutrophiles. On two occasions an electrocardiogram showed evidences of infarction of the anterior and apical portions of the left ventricle. During his hospital stay the patient continued to have severe pain, and on the thirteenth day he suddenly developed great gasping respirations and died. The heart sounds were muffled, as though from ventricular fibrillation. Death occurred twenty-three days after the onset of symptoms.

At autopsy the heart weighed 480 gm. There was massive, recent infarction of the anterior and apical regions of the left ventricle, the apex of the right ventricle, and approximately two-thirds of the anterior portion of the interventricular septum. The apex of the left ventricle bulged markedly to form an aneurysm 5 cm. in diameter which was filled with fresh thrombus.

One centimeter below the origin of the descending ramus of the left coronary artery was a soft, dark red blood clot which completely filled the lumen. Serial sections through this lesion revealed a large atheromatous plaque in which recent hemorrhage had taken place with the formation of an occluding hematoma. There was no thrombosis.

CASE 5584.—A white male, 55 years of age, was a business man, and, so far as his family and friends were aware, had been in good health until the day of death when he was shaken up in a slight accident. He was carefully examined by a physician immediately after the mishap and was thought to be unharmed. Six hours later he was found dead.

At autopsy moderately severe sclerosis of all branches of the coronary arteries was discovered. In the descending ramus of the left coronary artery, 3 cm. from its origin, was found a massive, annular hemorrhage in an atheromatous plaque, thus forming a large hematoma which completely occluded the lumen of the vessel. The hemorrhage was recent, with well preserved red blood cells, and the inner lining of the intima was everywhere intact (Figs. 5 and 6). There was no myocardial infarction.

CASE 5840.—A 48-year-old white woman, a housewife, was known to have had diabetes for five years. Twenty-two maternal relatives had had diabetes mellitus. Six months before her fatal illness the patient first complained of substernal pain, dyspnea, and edema on exertion. An electrocardiogram taken at this time was normal. She continued to have frequent attacks of anginal pain which were relieved only partially by nitroglycerin. Twelve hours before admission, following a profound emotional experience and after a ten-day period of intermittent precordial pain, the patient was seized with severe, excruciating, substernal pain which did not radiate and was not relieved by nitroglycerin.

The blood pressure was 140/85, the temperature 37.6° C., the pulse 120, and the respirations 35. The patient was obese, dyspneic, and slightly cyanotic, with quiet heart sounds and a regular pulse. The leucocyte count was 10,100, with a normal differential count. The electrocardiogram, taken on the day of admission, showed indications of myocardial damage with interventricular block, and sinus tachycardia, which were thought to indicate a posterior basal infarct with involvement of the interventricular septum. The patient's condition became steadily worse, and she died twelve days after the onset of the final attack.

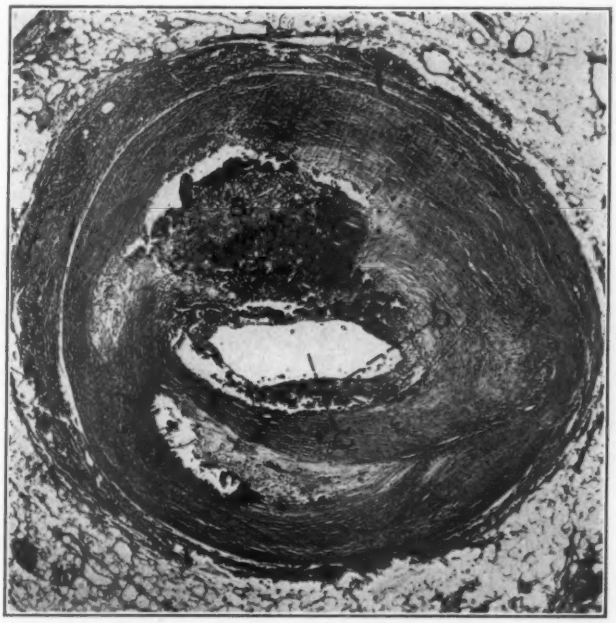

Fig. 5.—Case 5584. A section through the descending branch of the left coronary artery, showing massive hemorrhage, *a*, into the vessel wall. The endothelial lining, *b*, is intact, and the lumen, *c*, is patent.

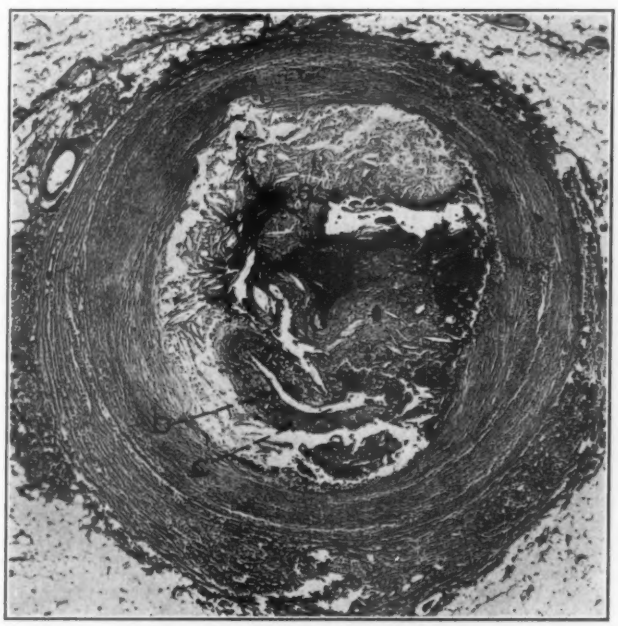

Fig. 6.—Case 5584. A section 3 mm. distal to Fig. 5. The lumen, *c*, is occluded because of compression by the intramural hemorrhage, *a*. The endothelial lining, *b*, is intact, and there is no thrombus.

At autopsy the heart weighed 335 gm. There was a recent, superimposed upon an organizing, infarct involving the left ventricle, particularly the posterior aspect, from the base to the apex and the posterior portion of the interventricular septum.

The left circumflex coronary artery was completely occluded by soft, dark red blood clot at a point 2 cm. from its origin. Serial sections showed massive recent hemorrhage into the wall of the artery with the formation of a hematoma which completely obliterated the lumen. The endothelial lining of the intima was everywhere intact, and there was no thrombosis. Both coronary arteries were the seat of severe sclerosis.

CASE 5928.—A 53-year-old negro, a laborer, had complained for nine months of shortness of breath and pain in the left upper quadrant. Fifteen years before the first admission a diagnosis of aneurysm of the transverse and descending portions of the aorta had been made. The Wassermann reaction was positive at that time. During the intervening years he was treated in the Out-Patient Department and was able to do the hard work of a laborer. He was also known to have diabetes mellitus, which responded well to treatment,

On admission to the hospital the blood pressure was 155/125, the temperature 38.6° C., the pulse 100, and the respirations 36. The patient was well developed and well nourished and did not appear seriously ill. The heart was greatly enlarged to the left, and two apical impulses were noted in the posterior axillary line, one in the fourth and the other in the fifth costal interspace. The blood and spinal fluid Wassermann tests were negative at this time although the Kline exclusion test was two-plus. X-ray examination indicated the presence of an aortic aneurysm.

An electrocardiogram showed that, since a record taken five years before, there had appeared changes in the S-T interval and T-waves of Leads I and III and more marked left axis deviation. These changes together with slurring of the QRS complex in Lead I and notching in Lead II were interpreted as indicating myocardial damage.

Three days before death the temperature increased to 40.4° C., the patient developed marked Cheyne-Stokes respiration and became disoriented. Signs of bronchopneumonia appeared in the right lung and the leucocyte count rose to 12,500. He died thirty-five days after admission to the hospital.

At autopsy the heart was greatly enlarged, and there was a fusiform and saccular aneurysm of the descending thoracic portion of the aorta with displacement of the heart, lungs, and esophagus. The aneurysmal sac was completely filled by thrombus —the so-called spontaneous cure.

The circumflex branch of the left coronary artery was occluded by soft, brownish red material at a point 2 cm. from the ostium. Serial sections through this area showed recent intramural hemorrhage with obliteration of the lumen by the resulting hematoma. The intimal endothelium was everywhere intact, and there was no thrombus.

In the right coronary artery, 5 cm. from the ostium, was an intramural hemorrhage which did not completely occlude the lumen but reduced it to an opening 1.5 mm. in diameter.

There was no evidence of recent myocardial infarction although occasional areas of fibrosis were encountered.

CASE 5929.—A white man, 62 years old, a picture framer, had complained for one week of transient attacks of severe precordial pain which radiated to the shoulders. During these attacks the patient noticed that he was short of breath.

The blood pressure was 190/100, the temperature 36.8° C., the pulse 60, and the respirations 40. The day before admission to the hospital the blood pressure dropped to 110/70, and the temperature increased to 39° C. The patient was suffering severe pain and was very apprehensive. Although the heart sounds were weak, they were regular and no murmurs were heard. There were no signs of congestive heart failure.

An electrocardiogram taken a few hours after admission to the hospital showed notching and slurring of the QRS complexes and elevation of the S-T intervals in Leads II and V. On the next day another record showed a decrease in the voltage of the QRS complex. The S-T interval in Leads I, IV and V had become elevated with inversion of the T-wave in Leads I and V. These changes were considered diagnostic of recent infarction of the anterior and apical portions of the left ventricle. During the following six days two other electrocardiograms were made. They showed a further decrease in the voltage of the QRS complex, with inversion of the T-wave in Leads II and III, and a decrease in the degree of inversion of the T-wave in the chest lead. These changes were considered consistent with the course of infarction of the apex and anterior wall of the left ventricle.

About three weeks after the onset of the illness, a pericardial friction rub developed and the leucocyte count rose to 13,700. The next day the patient became cyanotic, had a convulsion, and died.

At autopsy the heart weighed 530 gm. A large wedge-shaped mass of infarction was found in the anterior wall and apex of the left ventricle and the apical portion of the interventricular septum. Mural thrombus covered the necrotic myocardium.

The coronary arteries were the seat of severe sclerosis. One centimeter from its origin the lumen of the descending branch of the left coronary artery was very greatly reduced by an atheromatous plaque and occluded by dark red, friable material which seemed to have its origin in the plaque. The artery was occluded for a distance of nearly 1 cm. Microscopic sections through this region showed a large intramural hematoma which was undergoing organization. There was no thrombus.

CASE 5814.—A white male, 54 years of age, unemployed, but formerly a janitor, was well until three hours before admission when he awakened with severe stabbing pain, which originated substernally and radiated to the left shoulder, leaving the arm numb. The pain was continuous. In 1913 he had been told he had a leaky heart and noticed some dyspnea on mild exertion, but he had been able to work without difficulty.

The patient was prostrated, pale, sweating profusely, and complained of a sense of impending doom. The blood pressure was 80/30, the temperature 37.8° C., the pulse 77, and the respirations 22. The heart was weak and irregular, with quiet, distant sounds. There was marked dyspnea and ashen gray cyanosis. Three hours after admission the patient died while talking to the interne.

At autopsy the heart weighed 450 gm. The coronary arteries were the seat of severe sclerosis. Two centimeters from the ostium of the right coronary there was an ulcerated atheromatous plaque, 1 cm. in length, which on section oozed soft brownish red material and almost completely occluded the lumen. Serial sections showed massive recent hemorrhage into an atheromatous plaque (Fig. 7). At one point the intima was interrupted, and a small mural thrombus had formed (Fig. 8). The lumen was almost completely occluded by the hematoma and the mural thrombus. The myocardium showed a mild degree of fibrosis but no evidence of recent infarction. There was a moderate amount of fat infiltration in the right ventricle.

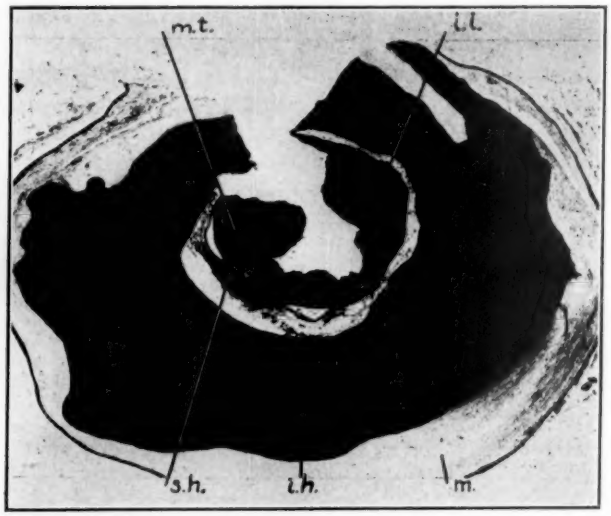

Fig. 7.—Case 5814. Diagram to illustrate the lesions found in the stenosed portion of the right coronary artery. At this level the intramural hematoma is covered by a narrow, intact layer of intima.

m.t., mural thrombus; *i.l.*, intact intima; *s.h.*, subendothelial hemorrhage; *i.h.*, intramural hematoma; *m.*, media.

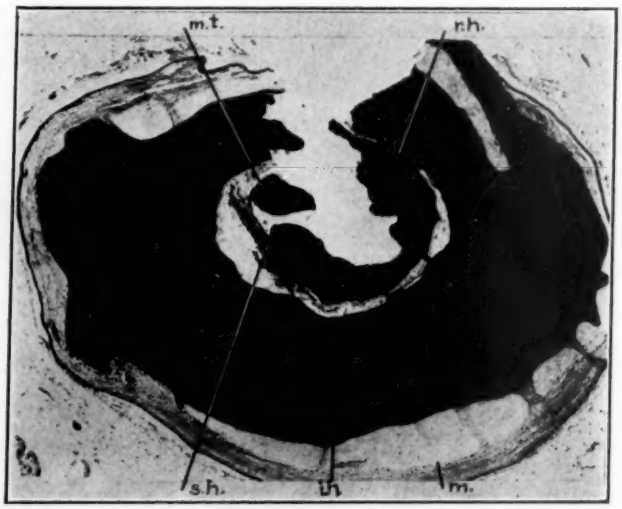

Fig. 8.—Case 5814. Diagram of a section of a few millimeters distal to Fig. 7, showing disruption of the intima.

m.t., mural thrombus; *r.h.*, rupture of hematoma into arterial lumen; *s.h.*, subendothelial hemorrhage; *i.h.*, intramural hematoma; *m.*, media.

SUMMARY OF FINDINGS

The clinical findings in these seven cases were for the most part those of myocardial infarction and coronary thrombosis. Most of the patients were in the sixth decade. One patient was a white woman and another a negro, but the others were white males. Many of the patients belonged to the laboring classes, although various occupations were represented. One-half of the patients had previously suffered from angina pectoris, but none had had symptoms for longer than ten months, and all died within five weeks of the onset of the final attack. Death occurred suddenly and unexpectedly in two patients (Cases 5584 and 5814), but with these exceptions all complained of precordial pain radiating to the arms. The usual signs and symptoms of myocardial infarction were present. Electrocardiographic records were obtained for five of the patients, and in these cases myocardial damage was shown by changes in configuration of the QRST deflections. In two cases it was possible accurately to localize the infarction (Cases 5561 and 5840). However, there were no characteristic electrocardiographic findings which permitted differentiation between intimal hemorrhage and true thrombosis.

The pathologic findings were similar in the seven cases. Severe intimal sclerosis with calcification and the formation of large atheromatous plaques were constant features. The lumen of one or more of the branches of the coronary arteries was blocked by soft, dark red blood clot, and serial sections of these areas revealed that the occlusion was not caused by thrombosis, as had been supposed on gross examination, but by hemorrhage into the wall of the artery. The hemorrhage was usually found in an atheromatous plaque (four cases) and except for one (Case 5814) was covered by a layer of intact endothelium. In no case was there bleeding into the media. The size of the hemorrhage varied but was usually massive, causing stenosis by actual compression of the lumen of the affected artery. In addition to the large hematoma, there were often multiple small hemorrhages scattered throughout the intima, especially beneath the endothelium. The intima in the region of the hemorrhage was always richly vascularized by capillaries which were frequently surrounded by focal accumulations of red blood cells. The age of the hematoma could not be accurately determined, but in many cases the excellent preservation of erythrocytes indicated recent origin. Sometimes, however, there was lysis of the red blood corpuscles and beginning organization and pigmentation.

Case 5561 illustrates a combination of lesions which was frequently observed in cases of coronary occlusion, namely, intramural arterial hemorrhage and recent thrombosis. The massive hemorrhage into an atheromatous plaque was easily made out (Fig. 7) and in most of the sections there was a narrow border of intact intima, separating the intramural hematoma from the lumen, but at one point the hemorrhage

had broken through the intima (Fig. 8). Thus, in addition to the large intramural hematoma, there was a recent thrombus within the lumen of the vessel. The significance of this combination of lesions will be discussed later in the paper.

An analysis of the incidence of the lesion in the various branches of the arteries shows that both arteries were involved in one case, the left coronary artery in five and the right in three cases. The commonest site of occlusion in the left coronary artery was just distal to the origin of the anterior descending branch (three cases). In one case it was in the circumflex branch near the midpoint. The right coronary artery was most frequently involved in the middle third (three cases).

The lesions produced in the myocardium were variable. Four cases showed recent infarction of the myocardium. The diseased muscle was easily recognized in the fresh specimen, and the usual histologic appearance of recent infarction was present. In three of the hearts there was no demonstrable myocardial infarction. This finding is explained in two cases by the fact that the patients died suddenly so that sufficient time had not elapsed for infarction to develop.

DISCUSSION

Although the finding of intramural arterial hemorrhage is an old observation, the lesion has received but little attention from most writers. Such hemorrhages are most commonly seen in the wall of the aorta but may affect any vessel. Recently Paterson[1] studied the vascularization and hemorrhage in the intima of arteriosclerotic coronary arteries and found hemorrhagic lesions within the intima in atheromatous foci in a number of arteriosclerotic coronary arteries, including those from nine patients with recent coronary thrombosis. He was able to demonstrate vascularization of the intima by discrete capillaries arising from the lumens of sclerotic coronary arteries and noted that when this intramural "hemorrhage was recent, capillary channels were found in the inner layers of the intima in close proximity to the extravasated blood."

Previously Benson[2] and Koch and Kong[3] had described breaks in the integrity of the intima of thrombotic coronary arteries permitting escape of blood between or into the coats of the artery and suggested that such changes might lead to the formation of a thrombus. Leary[4, 5] described the rupture of an atheromatous mass into the lumen of a coronary vessel with secondary thrombus formation. He has also described intimal capillaries arising directly from the lumen of the artery. Clark, Graef and Chasis[6] examined serial sections of eleven thrombotic coronary arteries. "The common observation was the presence of a fresh break in the fibrous lining of a lipoid plaque with penetration of blood elements into the atheroma. In other instances thrombus formation occurred on

an atheromatous plaque, in which thinning out and separation of the collagenous fibers of the lining plaque also had permitted infiltration of blood elements.''

Despite the fact, however, that intramural arterial hemorrhage has been frequently observed, the actual occlusion of a coronary artery by a hematoma formed entirely within the wall of the vessel and without thrombosis has not been previously described. In the gross this lesion is not easily recognized and might be interpreted as a thrombus. Even the microscopic examination of a few sections might not lead to the correct diagnosis. It is often necessary to examine serial sections through the whole of the occluded portion of the vessel in order to determine whether or not the intima is intact and whether the hemorrhage is entirely within the wall. When such a lesion is old and the only residuum is hemosiderin in an atheromatous plaque, the lesion could be misinterpreted as a canalized and organized thrombus.

In the present study serial sections of 41 occluded coronary arteries were studied, and of these, six (14.6 per cent) were caused solely by intramural hematoma. Fourteen (34.2 per cent) of the other cases showed a combination of intramural hemorrhage and thrombosis and one of these is included in this report because it illustrates the difficulty of determining whether the thrombosis is secondary to the rupture of a hematoma or whether the hematoma is the result of rupture of the intima and extravasation of blood beneath it. Several points, however, indicate that the former explanation is the correct one. If it be assumed that the thrombus formed first, then it is difficult to explain the formation of a hematoma in the wall of a vessel because, if the occlusion were complete, no blood could reach the affected portion or, if the occlusion were only partial, it would seem logical to assume that the mural thrombosis would protect the intima and tend to prevent the development of a hematoma. Again in some of the cases which have been studied, the hemorrhage within the vessel wall is of greater age than the thrombus, as indicated by the finding of hematogenous pigment within phagocytes and of beginning organization, whereas the thrombus shows none of these features.

It is no longer necessary to assume that bleeding into the wall of an artery is due solely to rupture of the intima and dissection beneath it by the blood stream, for Paterson[1] and Leary[4, 5] have convincingly demonstrated the origin of intimal capillaries from the lumen of a sclerotic artery. This finding has been confirmed by the present study, and it has also been possible to demonstrate vascularization of the atheromatous plaques by capillaries derived from the adventitia. It is easy to conceive that capillaries within an atheromatous plaque may rupture, for the soft, easily compressible material of the atheroma offers no support against the capillary blood pressure. Since patients with coronary arteriosclerosis frequently have hypertension, a small intramural capil-

lary might readily be ruptured and form a hematoma. With time such a hematoma could easily become large enough completely to close the lumen or even to rupture.

The site of rupture of a hematoma into the lumen of an artery would no doubt afford an excellent nidus for the development of a secondary thrombus. It has not been possible to demonstrate this convincingly, although many of the cases suggest strongly that the thrombus is secondary to a ruptured intramural hemorrhage. Winternitz, Thomas, and Le Compte[7] have recently suggested that hemorrhage derived from the intramural circulation may be an important factor in the development of arteriosclerosis. Further study may elucidate this problem.

SUMMARY

Six cases are described of complete occlusion of sclerotic coronary arteries by intramural arterial hemorrhage without thrombosis. An additional case is presented in which there was a combination of intramural hemorrhage and thrombosis of the left coronary artery. Death was directly attributable to the coronary lesion in all cases although in three there was no myocardial infarction. Attention is called to the probable importance of intramural arterial hemorrhage in the pathogenesis of coronary thrombosis.

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A STUDY OF ELECTRICAL ACTIVITY IN THE AURICLES*

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CONSIDERABLE data have been accumulated regarding the electrocardiographic effects of myocardial damage and aberrant excitation in the ventricles during the past few years. In contrast, however, the present knowledge regarding similar conditions in the auricles is rather scant. As yet no reports have appeared, to our knowledge, describing the electrocardiographic changes resulting from experimental injury to the auricular myocardium; and there is some controversy concerning the relationship of the site of ectopic excitation in the auricle to the form of the resulting aberrant P-wave.

Recently the subject of duration of electrical activity in the auricles has received renewed attention. As pointed out by Wedd and Stroud,[1] the onset of the P-wave heralds only approximately the initiation of the period of invasion, for a low grade electrical potential difference indicating activity in the vicinity of the S-A node exists before this inflection is inscribed. Further, the termination of the P-wave can no longer be considered to represent the completion of the period of electromotive changes, since a deflection has been described following the P-wave, which has been proved to be bound up with electrical recession in the auricles. This deflection, designated as the Ta wave by Hering,[2] is generally opposite in direction to the P-wave, but is usually obscured by the aftercoming ventricular complexes.

In the present investigation, it was therefore decided to study the electrocardiographic changes resulting from (a) cauterization of various sites on the auricular wall, and (b) the production of artificial premature auricular contractions. It was hoped that by comparing the curves resulting from the two procedures a correlation might be found to exist analogous to that observed in our study of the ventricles under similar conditions.‡ [3, 4] Further, it was thought that by the introduction of a constant current of injury (as a result of cauterization) some information might also be obtained as to the actual duration of electrical events in the auricles. With this point in mind, and to obliterate possible

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‡In the case of the ventricles, it was found that the direction of the initial main deflection of the extrasystolic wave was inversely related to the direction of the RST deviation obtained with normal sinus rhythm, when the site on the ventricle from which the premature contraction arose was subsequently cauterized.

electrocardiographic changes caused by the presence of ventricular complexes, it was decided to produce complete heart-block in several of the animals prior to cauterization.

The data obtained by the above procedures form the basis for this report.

METHOD

The following data were obtained from experiments on six cats and five dogs, anesthetized by "dial" injected intraperitoneally (0.6 c.c. per kilo). Artificial respiration was instituted, the sternum and portions of adjoining ribs and cartilages

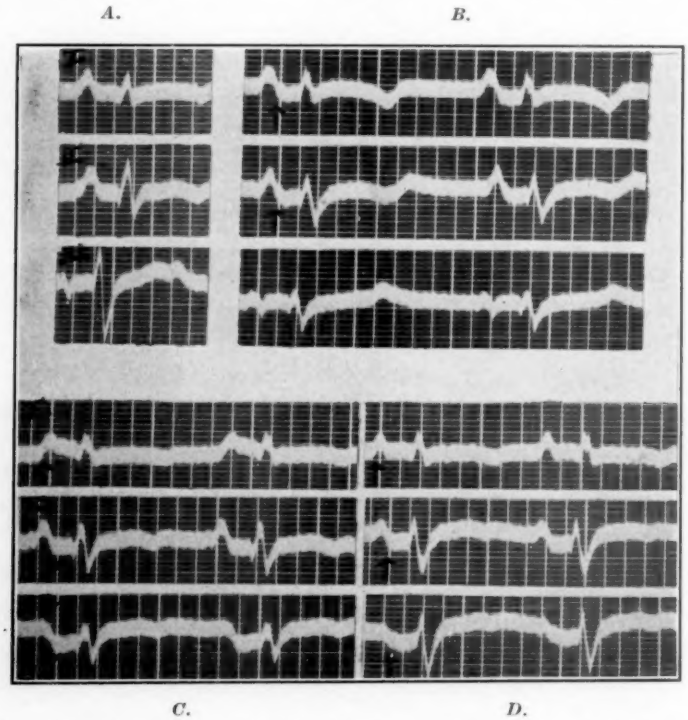

Fig. 1.—Cauterization of auricles in the dog (dog 1). *A*, Control records, *B*, Cauterization of right auricle. Depression of P-Ta interval in Leads I and II and no change in Lead III. *C*, Cauterization of left auricle about ten minutes after "B." Elevation of P-Ta interval in Lead I and depression in Leads II and III. *D*, Cauterization of both auricles about twenty minutes after "C." P-Ta interval back in normal isoelectric position in Lead I and depressed in Leads II and III. Arrows indicate changes in position of P-Ta interval. Vertical time lines—0.04 second.

were removed, and the entire heart was exposed by slitting the pericardium. The cut edges of the latter were then sewed to the chest wall so as to form a hammock and thus maintain the heart in a constant experimental position. Control electrocardiograms were obtained before opening the chest and after exposing the heart. In some experiments first one and then the other branch of the Bundle of His were cut in order to induce complete heart-block. In all but two cases, a cautery was applied to specific portions of the auricles so as to produce an injury which extended as deeply as possible into the auricular wall without penetration of the cavity. After the lesion was produced, cotton pads were placed lightly over the

heart, the sternum was replaced and an electrocardiogram was immediately taken. If no obvious change was noted, the cauterized area was extended until definite alterations were observed. In most experiments it was found possible to reapply the cautery later to a different site in the auricular wall for further observations.

Prior to cauterization, in four of the experiments on dogs, premature auricular contractions were elicited by stimulating various sites on the auricles with single minimal induced shocks sent in at different times in the cardiac cycle.

Since all complexes in Lead I were generally of low amplitude, it was decided to increase the sensitivity of the string so that the introduction of one millivolt caused a deflection of two centimeters. The other two leads were obtained with conventional standardization, i.e., 1 cm. = 1 mv.

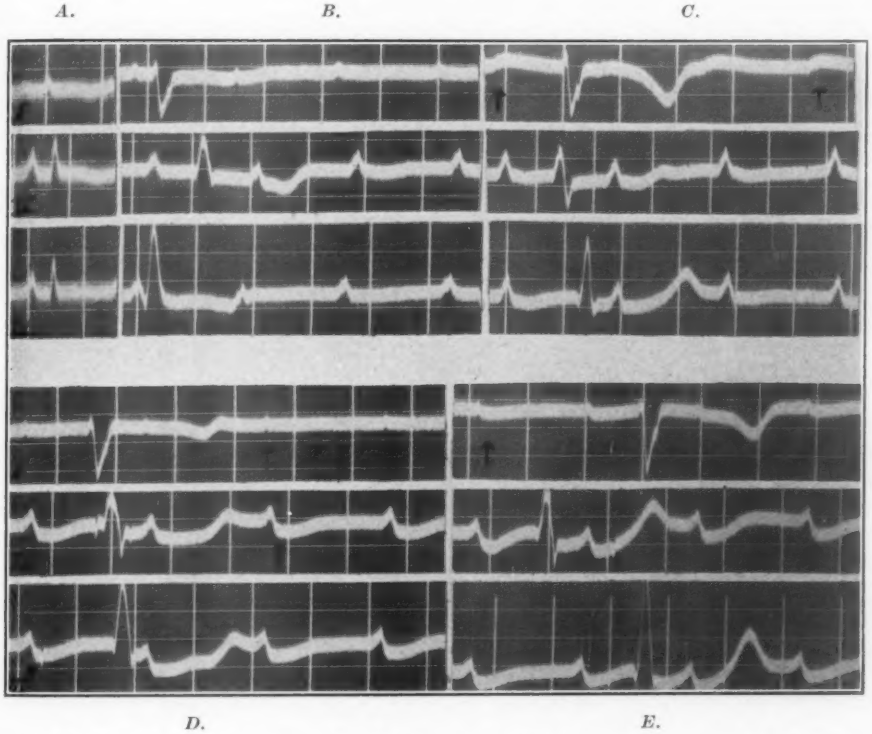

Fig. 2.—Cauterization of auricles in the cat (cat 1). *A*, Control record. *B*, Complete heart-block produced by cutting first the right and then the left branch of the Bundle of His. *C*, Cauterization of the left auricle. Elevation of P-Ta interval in Lead I and no change in Leads II and III. *D*, Cauterization of both right and left auricles. P-Ta interval back in normal isoelectric position in Lead I and markedly depressed in Leads II and III. *E*, Further cauterization of right auricle about ten minutes after "D." Depression of P-Ta interval in all three leads. Arrows indicate changes in position of P-Ta interval. Vertical time lines—0.2 second.

RESULTS

I. Cauterization of Auricular Wall

Upon cauterization of the auricular wall, an elevation or depression of the normally isoelectric interval between the end of the P and the beginning of the R-wave was consistently noted (Figs. 1 and 2). This portion of the electrocardiogram (which may be considered to be the

counterpart of the RS-T segment of the ventricular grouping) will hereafter be designated as the P-Ta segment, since it lies between the P-wave, which indicates auricular excitation, and the Ta-wave (obscured by the R-wave) which indicates auricular retreat. Conformity is thus maintained with ventricular terminology.

In many cases the P-wave was affected by the cauterization as well as the P-Ta segment, although not as conspicuously (Fig. 1). The modifications of the P-wave consisted either of an increase or decrease in its height, with slight changes in contour. In those records in which an

TABLE I

EXPERIMENT NUMBER	AURICLE CAUTERIZED	EFFECT OF CAUTERIZATION UPON P-Ta INTERVAL			DURATION OF P-R INTERVAL BEFORE COMPLETE HEART-BLOCK	DURATION OF P-WAVE AND P-Ta CHANGE AFTER INJURY, IN THOSE CASES WITH COMPLETE HEART-BLOCK
		LEAD I	LEAD II	LEAD III		
Cat 1-A	Left	+	0	−	.08 second	.18 second
Cat 1-B	Right and Left	0	=	=	.08 second	.21 second
Cat 1-C	Right	−	=	=	.08 second	.23 second
Cat 2	Left	+	−	−		
Cat 3-A	Right	=	=	=		
Cat 3-B	Left	+	−	=		
Cat 4-A	Right	−	0	0		
Cat 4-B	Left	+	−	−	.06 second	.12 second
Cat 5	Left	+	−	−	.09 second	.15 second
Cat 6	Right and Left	+	−	−	.08 second	.17 second
Dog 1-A	Right	−	−	0		
Dog 1-B	Left	+	−	=		
Dog 1-C	Left and Right	0	=	=	.09 second	.14 second
Dog 2-A	Right	=	=	−		
Dog 2-B	Left	+	=	=		
Dog 3-A	Right	0	−	−		
Dog 3-B	Left	+	=	=	.08 second	.13 second

\+ P-Ta segment displaced in a positive direction.

\- P-Ta segment displaced in a negative direction. The number of these represents the relative magnitude of the displacement.

0 No effect upon the P-Ta segment.

elevation of the P-Ta segment was present, the downstroke of the P became fused with the first portion of the P-Ta segment (Fig. 1-*C*); in a manner similar to the change observed in the ventricular curve following ventricular trauma (the R-T transition arising high up on the descending limb of the R-wave). When a depression of the P-Ta interval was present, it was generally written only after the descending limb of the upright P-wave had crossed the isoelectric line (Fig. 1-*B*). In cases where the P-wave was small and the P-Ta change comparatively greater, the P-wave often lost its identity in the latter (Fig. 2-C).

Changes in Lead I.—Examination of Table I reveals that in all instances, following cauterization of the left auricle, the P-Ta interval in Lead I became elevated from its previous isoelectric position (Figs. 1-*C* and 2-*C*) while in all instances of cauterization of the right auricle (except in one case in which no change was manifest) a depression of the P-Ta interval was obtained (Figs. 1-*B* and 2-*E*) in that lead. Changes in the site of the trauma, so long as it was limited to the same auricle, did not affect these results. Thus cauterization of either the anterior or posterior surface of the right auricle uniformly produced a depression of the P-Ta segment, while cauterization of comparable sites in the left auricle caused an elevation of the P-Ta segment.

Further evidence on the relationship of site of trauma to the electrocardiographic alteration in Lead I was observed in two experiments (cat 1 and dog 1) in which first one, and then the other, or both auricles were successively injured. In one (dog 1 in Fig. 1) with cauterization of the right auricle, there was a depression of the P-Ta segment in Lead I, which was followed by a reversal to an elevated position when the left auricle was subsequently injured. After a twenty-minute interval, both auricles were again simultaneously cauterized, whereupon the P-Ta segment returned to an isoelectric position. In the other instance (cat 1 in Fig. 2) the left auricle was first cauterized, with a consequent elevation of the P-Ta segment in Lead I, which then became isoelectric when this procedure was applied to both auricles. Following this with more extensive cauterization of the right auricle, a depression appeared. In both cases the return of the P-Ta segment to the isoelectric line with simultaneous cauterization of the two auricles apparently was not due to a disappearance of the transient current of injury (for at the same time Leads II and III in each instance manifested definite indications of its presence (Figs. 1-*D* and 2-*D*), but rather to the neutralizing effect of the electrical disturbances produced in one auricle upon those consequent to cauterization of the other. One is justified in stating, therefore, on the basis of the above, that the site of cauterization, as to the right or left auricle, will determine the type of alteration of the P-Ta segment observed in Lead I.

Changes in Leads II and III.—The changes in Leads II and III, upon cauterization of either auricle, uniformly consisted of a depression of the P-Ta segment, regardless of whether the anterior or the posterior surface was the site of the lesion (Figs. 1 and 2). In rare instances, no alterations were noticed in these leads, despite changes in Lead I; the reverse also being true in other cases. No localizing signs could therefore be obtained from an examination of the changes in the position of the P-Ta segment in Leads II and III.

Comparison of the Normal P-R Interval With the Combined Duration of the P-Wave and P-Ta Displacement Change in Complete Heart-

Block.—With normal sinus rhythm following auricular cauterization, the P-Ta displacement was seen to end abruptly with the onset of the more prominent QRS complex. In order to determine whether or not the displacement actually persisted beyond the ventricular complex, complete heart-block was produced in four cats and two dogs (Table I), and the normal P-R interval was then compared with the combined duration of the P-wave and P-Ta displacement change, after the injury. Whereas the P-R interval in the cat and dog ranged between 0.06 and 0.09 second, the combined P-wave and P-Ta deviation ranged between 0.12 and 0.23 second (Fig. 2) or much longer than the P-R interval. The significance of these findings will be discussed later.

II. Production of Auricular Premature Contractions

Changes in Lead I.—In four experiments on dogs, premature auricular contractions were elicited from various sites on the epicardial surface of both auricles prior to cauterization of one of these sites. It was found that on stimulation of the right auricle the aberrant P-wave in Lead I was almost consistently positively directed (Fig. 3). This held for sites on the anterior, lateral, and posterior surfaces, as well as for superior, middle, and inferior levels, the only exception being one instance of stimulation on the lateral surface inferiorly from which a diphasic P-wave was obtained. In each of the four experiments eight sites on the right auricle were examined.

On stimulation of the left auricle, the aberrant P-wave in Lead I was generally negative (Fig. 4), although in a number of instances it was difficult to decide upon its exact direction because of small amplitude or distorting effects of the "stimulus escape." Sites on the anterior, lateral, and posterior surfaces at different levels were likewise studied. In one experiment, ten areas were stimulated and in all cases in which the results were decisive (six) they conformed to the above generalization. This was also true in the other three experiments in each of which six areas were examined.

Changes in Leads II and III.—The aberrant P-waves in Leads II and III resulting from stimulation of the right and left auricles, while infrequently variable, were usually positively directed for all sites on both auricles (Figs. 3 and 4).

III. Comparison of Curves Produced by Auricular Trauma and Premature Contractions

The results of the subsequent cauterization of the auricles in two of the last described experiments conformed with the findings already described (Table I). Comparison of the electrocardiographic records of the two procedures (i.e., first the production of ectopic auricular

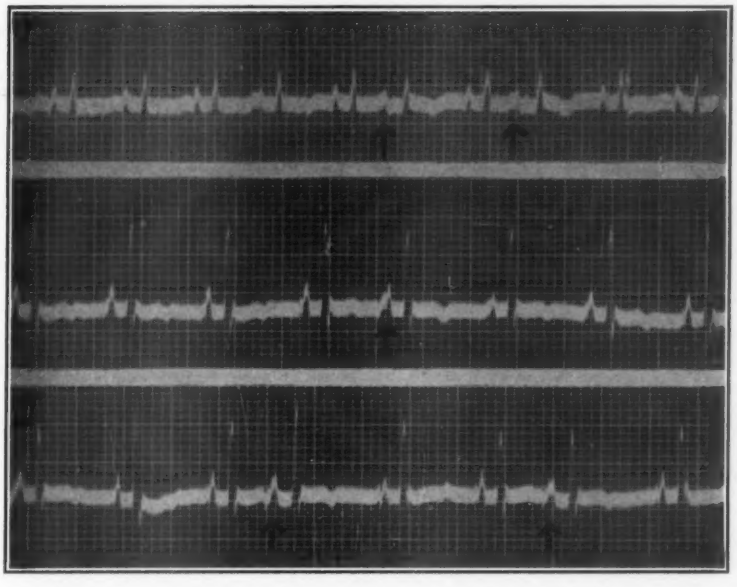

Fig. 3.—Auricular premature contractions produced by stimulation of right auricle in the dog. Arrows indicate the aberrant P-wave followed by a supraventricular complex and under compensatory pause. The aberrant P-wave is upright in all three leads. Vertical time lines—0.04 second.

Fig. 4.—Auricular premature contractions produced by stimulation of the left auricle in the dog. Arrows indicate the aberrant P-wave followed by a supraventricular complex and under compensatory pause. The aberrant P-wave is inverted in Lead I and upright in Leads II and III. Vertical time lines—0.04 second.

beats from a specific site and then cauterization of this site) revealed that whereas the aberrant P-waves in Lead I were positively directed for sites on the right auricle, the displacement of the P-Ta interval (with normal sinus rhythm) following cauterization of this auricle was negatively directed. A similar type of relationship held for the left auricle, except that here the direction of the aberrant P-wave was negative and the P-Ta segment positive. In reference to Lead II and Lead III, the P-Ta interval was generally depressed for sites of trauma on either right or left auricle, while the aberrant P-waves were positively directed. The significance of these findings will be discussed.

DISCUSSION

It is generally conceded that when the ventricular myocardium is traumatized, the resulting current of injury manifests its presence by a displacement of the RS-T segment from its normally isoelectric position. Actually, of course, this change represents a temporary negative variation of the injury current, i.e., a tendency toward the neutralization of that current when the charges of normal excitation are present in the intact muscle surrounding the injured region. Although the negative variation of the current of injury exists from the beginning of activation to the end of recovery, the QRS complex is very little affected because of its relatively greater electrical magnitude, and thus the only obvious change is seen in an alteration of the RS-T segment and possibly a distortion of the T-wave as well.

From an examination of the present results, parallel conclusions to the above can be drawn for the electrocardiographic representation of auricular electrical events. First, to discuss the normal curve, there is a wave which can be considered roughly to indicate the onset of invasion, the P-wave, which is followed by an isoelectric interval, the P-Ta segment, during which period there is a state of balanced activity or temporary neutralization of potential differences throughout the auricles. The period of retreat or recovery is then represented by the Ta-wave, but since the electrical events during this stage are of small magnitude, the wave is either lost in the much greater electrical effects consequent to activation of ventricular muscle, or if written before the latter takes place, it is of such small amplitude as to be generally invisible. However, if auricular muscle is traumatized, a factor is introduced which tends to alter the relationship and contour of the waves so long as the tissue remains in a dying state. For now normal excitation of auricles injured locally results in a negative variation of the existing current of injury, which takes the form of a displacement of the P-Ta segment.*

*The constancy with which P-Ta segment changes in the dog and cat followed the production of auricular damage leads one to believe that possibly close examination of the comparable portion of the human electrocardiogram might be of value in those instances in which the rare clinical condition of auricular infarction with rupture is suspected. Although a number of such cases have been reported,[5] in only two were electrocardiographic records included; these, however, showed no definite changes.

This negative variation of the current of injury is present during the entire period of auricular activity, i.e., during invasion, balanced activity, and retreat, and, if of sufficient magnitude, it may affect the contour of the P-wave as well as the P-Ta segment and the Ta-wave. Moreover, the point at which the displaced P-Ta segment returns to the isoelectric line will serve to indicate the termination of the period of auricular activity, and thus the relative position of the normally invisible Ta-wave.

In this connection it is of interest again to call attention to the finding that the combined duration of the P-wave and displaced P-Ta interval, measured after cauterization and complete heart-block had been produced, was much greater than the normal P-R interval (Table I). In other words, it would appear from this that the electrical disturbances related to the terminal portion of the recovery period in the auricles are present but ordinarily obscured when the much greater changes due to the onset of ventricular activity are recorded. Only when the effects of the latter are eliminated, as by the production of complete heart-block, can the full extent of auricular activity be readily visualized by means of traumatizing the auricles. These observations are in accord with those of Brown,[6] who utilized esophageal leads to obtain his data. It was his opinion that records obtained by esophageal leads are akin to electrograms and therefore give more accurate data as to the onset and duration of activity in the auricles than do the standard electrocardiograms. With this method he found that the Ta-waves in the esophageal curves extend well into the period in which the QRST waves are written and frequently exert some influence on the RS-T segment.

As has been stated before, examination of the electrocardiographic records of experimental premature auricular contractions reveals that stimulation of the right auricle produced upright aberrant P-waves in Lead I, whereas stimulation of the left yielded negative deflections. This is understandable if we compare the two auricles to a single hollow tube of muscle lying across the chest, grossly parallel to the lead line of Lead I, and being excited at one or the other end. In those instances, then, in which the impulse arises in the right auricle, either in its normal site, the sino-auricular node, or in some ectopic focus, its predominant direction of spread would be across the auricles from right to left, and thus a positive deflection would be recorded in the conventional Lead I. The reverse, of course, would hold for premature auricular impulses arising in the left auricle, and consequently negative deflections would be obtained. As expected under these conditions, the level at which the excitation wave originated (i.e., with respect to the upper or lower portions of the auricles), in the dog at least, did not significantly influence the contour of the ectopic P-wave in Lead I.

Comparable conclusions to the above could not be drawn for Leads II and III since the type of curve was generally the same in both leads (upright aberrant P-waves) no matter in which auricle, or on which surface, the ectopic focus was situated.

As in the case of analogous curves in the ventricles, the direction of the aberrant P-wave bears an inverse relation to the direction of the displaced P-Ta segment, when the site which was previously stimulated is then cauterized. Thus, as has been stated before, in right auricular stimulation, aberrant P-waves were obtained which were upright in Lead I and inverted in Leads II and III, while cauterization of the area from which the ectopic impulses arose resulted in P-Ta plateaus which were depressed in Lead I and elevated in the other two. The explanation which has been applied to similar phenomena in the ventricles[4] can equally well be utilized for the changes in the auricles; for in brief it depends upon the fact that both excitation and injury of tissue develop relative negativity at the site of application and are thus in the same phase. Since the P-Ta displacement represents the negative variation of the current of injury (i.e., is opposite in sign to the latter) it must also be inverse in direction to the aberrant P-waves obtained by previously stimulating the region.

SUMMARY

The electrocardiographic changes following artificial stimulation and cauterization of the auricles were studied in a series of six cats and five dogs.

It was found that on cauterization of the auricular wall, a displacement in the position of the normally isoelectric line present between the P and R-waves, was consistently produced. This portion of the electrocardiogram, designated as the P-Ta segment, became elevated in Lead I when the left auricle was the site of injury and depressed in this lead on cauterization of the right auricle. In Leads II and III, the P-Ta segment assumed a depressed position regardless of which auricle was traumatized. The changes in the position of the P-Ta segment were considered to represent the negative variation of the auricular current of injury and the type of alteration was compared with that observed in the R-T transition following damage to ventricular muscle.

It was found that the P-Ta segment change produced by auricular trauma did not end with the onset of the R-wave, but instead extended for some time into the period of ventricular activity. This observation confirmed the view, held by other investigators, that under normal conditions the terminal portion of the recovery period of auricular activity is not ordinarily visible in the electrocardiogram since it occurs during the period in which the ventricular complexes are inscribed.

Upon artificial stimulation of the auricles, it was found that the direction of the aberrant P-wave in Lead I generally depended upon the lo-

cation of the site of origin as to one or the other auricle; being positive for instances of right auricular excitation and negative for left. In Leads II and III, the aberrant P-wave was positively directed for all sites on both auricles.

When the results of stimulation and cauterization of the same site were compared, it was observed that the direction of the aberrant P-wave had an inverse relationship to the direction of the displaced P-Ta segment (obtained with normal sinus rhythm).

We wish to express our gratitude to Mr. Joseph Marrus for his technical assistance in carrying out the preliminary experiments.

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CONGENITAL TRANSPOSITION OF THE GREAT ARTERIAL TRUNKS*

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THE publication of records of unusual congenital cardiac defects is of value in augmenting the literature available to workers who are particularly interested in this phase of heart disease. Congenital heart disease should be of more than academic interest. Recognition of the presence of these abnormalities in the living patient is of great practical value, and can be achieved only by constant clinical alertness and by the correlation of information obtained at post-mortem examination with physical signs and symptoms.

Transposition or incomplete torsion of the great arterial trunks consists of an alteration of the relations of the vascular trunks to each other and to the ventricles from which they normally arise; it is the result of a failure of normal rotation to occur during the early stages of cardiac development. Simultaneous with formation of the septum and with division of the heart into its chambers, there is a division and torsion of the common arterial trunk. The result of incomplete torsion is congenital transposition of the arterial trunks. Normally, the rotation proceeds clockwise and eventually describes an angle of 180 degrees, which is the mechanism that determines the relative positions of the pulmonary artery and aorta in the fully developed normal human heart; that is, the pulmonary artery arises from the right ventricle and anterior to the aorta. It is evident that if the process of torsion is impeded in its course or is not completed, any combination of positions of the pulmonary artery and aorta may result.

Rokitansky[1] recognized and described three types of transposition and his classification was used until Spitzer's observations[2] were published and his classification was adopted. In Rokitansky's classification, dextroposition of the aorta was considered as an entity apart from the group of anomalies classified under transposition, but Spitzer classified dextroposition of the aorta as Type I Reitende Aorta. This anomaly consists of an aorta that occupies a straddling position over a septal defect and receives blood from both ventricles. Type II of the classification of Spitzer corresponds to partial transposition as classified by Rokitansky in which both vessels, the aorta and pulmonary artery, arise from either ventricle, and is associated with a septal

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defect. The vessels may be stenosed or dilated but rarely are they of normal caliber. If this anomaly is accompanied by a pulmonary artery of normal caliber, it constitutes another anatomical complex, intermediate between Fallot's tetralogy and Eisenmenger's complex; the former is associated with a stenosed pulmonary artery and the latter with a dilated pulmonary artery.

Type III of Spitzer's classification includes cases in which no degree of torsion has occurred, and represents complete transposition in the classification of Rokitansky. In this type, the arteries have a relation-

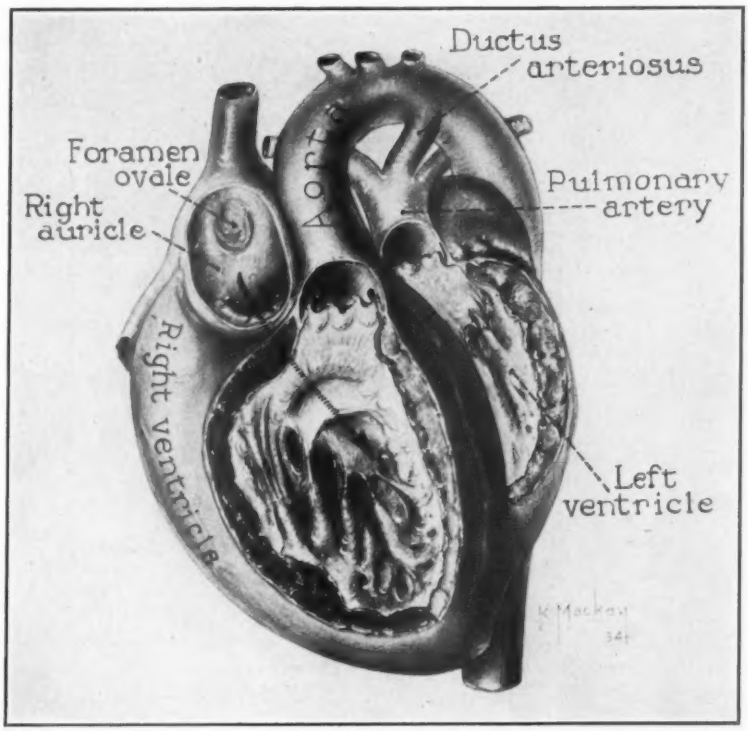

Fig. 1.—Diagram of the heart in Case 1. Complete transposition of the great vessels.

ship that is opposite to that of the normal one; that is, the pulmonary artery arises from the left ventricle and the aorta originates from the right ventricle. In these cases there may or may not be an associated interventricular septal defect.

Spitzer described Type IV as an anomaly comprising the complete defect of the interventricular septum in the cor biatriatum triloculare.

INCIDENCE

Of the 1,000 cases reviewed by Abbott[3] there were recorded 69 cases of transposition in which this lesion was uncomplicated. Fifty-three of these 69 cases were classified as complete and 16 as partial trans-

position. Abbott stated in her 1932 monograph that there occurred only ten instances of partial transposition in which both vessels were of normal caliber.

Of the 87 major cardiac anomalies observed at The Mayo Clinic, there were five instances of transposition of the great arterial trunks.

REPORT OF CASES

CASE 1.—A white girl was born twenty days before admission. No evidence of attacks of cyanosis nor convulsions was given in the history. Forceful vomiting had occurred occasionally. The day before admission the infant had become fretful, nursed poorly, and the stools were of a loose consistency. Dyspnea and cyanosis developed and increased rapidly in severity. Examination revealed a child acutely ill, cyanotic, and gasping for breath. No physical findings referable to the heart were recorded. Oxygen was administered with no apparent improvement of her condition and the child died thirteen and a half hours after admission.

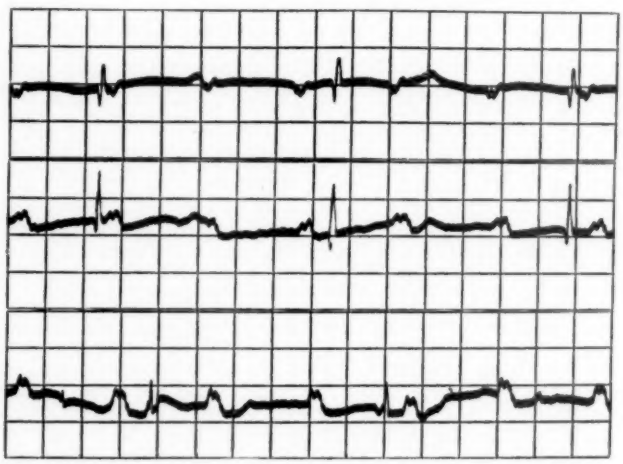

Fig. 2.—(Case 2). Electrocardiogram. Complete auriculoventricular dissociation.

At necropsy the heart was examined and weighed 50 gm. Externally no gross abnormalities were observed except that the right ventricle was more prominent than usual. The aorta originated from the right ventricle. This vessel was identified by the origins of the coronary arteries which were normal. The ductus arteriosus was patent and its lumen measured 2 mm. The pulmonary artery originated from the left ventricle and pursued its usual course. The venous structures were normal. The thickness of the right ventricular wall was 0.5 cm.; that of the left ventricular wall was 0.8 cm. The interventricular septum was intact and the foramen ovale was closed by a thin membranous flap. The aorta was to the right and in front of the pulmonary artery (Fig. 1).

CASE 2.—A white boy who had been delivered at full term was admitted for examination. His delivery was normal and his birth weight was 7 pounds and 3 ounces (3.3 kg.). Examination at birth revealed fair color, absence of the left external auditory canal and a rudimentary left ear; there was a dermoid at the temporal limbus of the left eye, the face was drawn to the right side and a cyst derived from the left branchial cleft was present. A systolic murmur, which became more pronounced shortly before death, was heard over the base of the heart; the

pulse was irregular and the rate was sixty beats per minute. The electrocardiogram indicated the presence of complete auriculoventricular dissociation (Fig. 2). Roentgenographic studies indicated that the stomach was in the right side of the abdominal cavity (situs inversus). Also a widening of the upper mediastinal shadow toward the right side of the thorax probably represented the thymus gland. The child failed to gain and marked cyanosis developed. On the eighteenth day after birth breathing became shallow and rapid, the cyanosis deepened, and the child died.

At necropsy the heart was found to occupy a normal position but the aorta curved downward on the right side. The heart was globular in shape, apparently equally divided into right and left ventricle. The endocardium appeared normal. The pulmonary veins entered the right auricle which appeared normal. The right auricle communicated with the right ventricle through a normal tricuspid valve. The foramen ovale was partly closed by a fenestrated membrane. The ductus arteriosus was patent; its lumen measured 3 mm. in diameter. The venae cavae entered the left auricle which communicated with the left ventricle by a normal mitral valve. The left ventricle gave origin to the pulmonary artery which had a bicuspid valve. The systemic aorta originated from the right ventricle and had normal valves and coronary origins. The aorta occupied a position to the right of, and anterior to, the descending aorta. There was an interventricular septal defect which measured 3 mm. in diameter.

Case 3.—A normal boy, born at full term three months before, was brought for examination. His delivery had been spontaneous and his weight at birth had been 8 pounds (3.6 kg.); he had been cyanotic since birth. He had nursed well and had gained weight until one week before his admission to the hospital. At the time of his admission he was acutely ill, with cyanosis of the lips and fingers. Respiration was rapid and shallow and a systolic murmur was audible over the base of the heart, with its maximal intensity over the sternum. Scattered râles were heard over the entire thorax. Roentgenologic examination gave evidence of enlargement of the heart. The child was placed in an oxygen tent. His condition temporarily improved, then became progressively worse and he died six days after admission.

At necropsy the heart weighed 61 gm. and was brownish pink in color. There was no increase in epicardial fat. The right auricle appeared slightly dilated. The tricuspid valve appeared normal. The aorta was identified by the origin of the coronary arteries which arose in a normal manner. The aorta issued from the right ventricle and its orifice was normal. The pulmonary artery arose from the left ventricle and communicated with the aortic arch by a patent ductus arteriosus. The foramen ovale was open and the interventricular septum was intact. The vena cava and pulmonary veins were in normal relationship to the auricles. The pulmonary artery was to the right of, and anterior to, the aorta.

Case 4.—A white boy, one month of age, whose birth had been normal, was admitted to the clinic. Cyanosis had not been noticed until three days after birth. Respiratory difficulty had developed at that time and roentgen therapy had been instituted on the basis of the diagnosis of an enlarged thymus. At the age of ten days, enlargement of the heart had been apparent and a murmur had been heard. Examination at the time of admission revealed an acutely ill child gasping for breath and markedly cyanotic. A systolic murmur was heard over the apex of the heart and râles were heard over the bases of both lungs posteriorly. An electrocardiogram gave evidence of marked right ventricular preponderance, and the P-waves were exaggerated in Lead II. The patient gradually failed in health, and death occurred two days after admission.

At necropsy the heart weighed 70 gm. and its color was brownish red; there was no excess epicardial fat. The ventricles appeared to be equal in size. The

right auricle received the venae cavae in a normal manner and communicated with the right ventricle through a normal tricuspid valve. The aorta arose from the right ventricle and its orifice was guarded by three normal semilunar cusps. The coronary arteries arose behind these cusps, one from the left sinus of Valsalva, and one from the posterior sinus. The pulmonary artery arose from the left ventricle and communicated with the aorta by a patent ductus arteriosus. The cusps of the pulmonary artery were normal in position and structure. The foramen ovale admitted a probe. The aorta was at the right of and anterior to the pulmonary artery. The interventricular septum was intact.

CASE 5.—A well-developed white boy, seven months of age, was admitted for examination. His birth had been normal, no difficulty in resuscitation had occurred, and there had been no cyanosis. He had progressed well for two months and then had begun to have vomiting spells accompanied by cyanosis. Roentgen therapy

Fig. 3.—(Case 5). Both aorta and pulmonary artery arising from the right ventricle; both vessels are of normal caliber.

applied over the thymus did not improve his condition. Roentgenological studies at that time revealed the stomach to be on the right side of the abdominal cavity. Response to treatment for pyloric obstruction was poor and the patient was removed to a hospital. At the time of admission the child was poorly nourished, mentally alert, but with dusky skin. A systolic murmur was heard over the base of the heart and the murmur was not transmitted. While the patient was in the hospital, otitis media and bronchopneumonia supervened and he died three weeks after admission.

At necropsy the heart occupied its normal position in the thoracic cavity, weighed 100 gm., and was reddish brown. It was globular in shape and appeared to have a large right ventricle and a small left ventricle. The consistency of the muscle was normal. There was no streaking in the muscle layer and the appendages, endocardium, and valves were normal. The inferior and superior venae cavae originated in the right auricle, in their normal positions. The coronary sinus was also in normal position. The foramen ovale was closed except for a slit-like patency

which was well guarded by a thick membranous flap. The cavity of the right ventricle was approximately five times the size of the left. The tricuspid valve measured 5.5 cm. and was normal in its relationships. The wall of the right ventricle measured 1 cm. in thickness while that of the left measured 0.75 cm. Both the pulmonary artery and the aorta were of normal caliber and arose in the right ventricle (Fig. 3). The aorta was identified by the origins of the coronary arteries which were in normal position. The aorta was situated to the right of and dorsal to the pulmonary artery. The ductus arteriosus was represented by a mere fibrous cord and there was a dimpling of the intima of both the aorta and pulmonary artery over the respective points of junction with the ductus arteriosus. The left auricle received the pulmonary veins and communicated with the small left ventricle through the mitral orifice which was guarded by a competent bicuspid valve which measured 3 cm. There was no point of exit from the left ventricle except by way of a patent interventricular septum; this opening measured 1 cm. in diameter and represented complete absence of the membranous septum (Fig. 4). The valves of

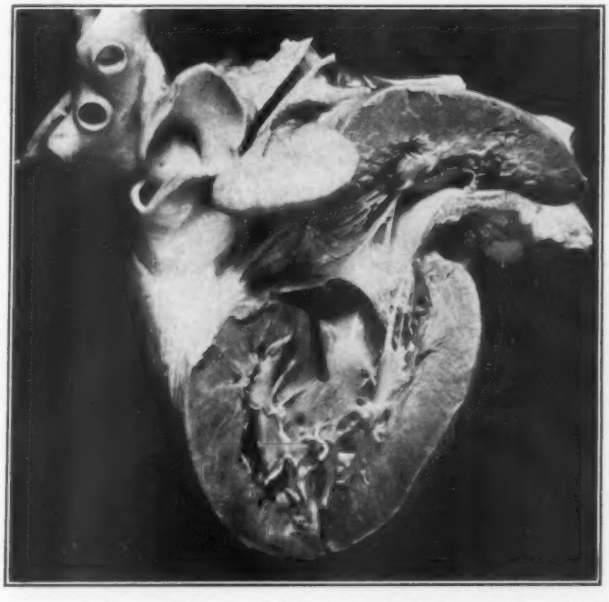

Fig. 4.—(Case 5). The same heart as that represented in Fig. 3 viewed from the left ventricle. A probe extends through the interventricular septal defect.

the aorta and the pulmonary artery were normal and there was no stenosis nor dilatation of either vessel. A blood vessel which measured 3 mm. in diameter originated from the posterior surface of the arch of the aorta. The destination of this blood vessel could not be determined. The blood vessel may have represented the remnants of the fourth left aortic arch.

This case represents Type II of Spitzer's classification or a partial transposition according to the older nomenclature of Rokitansky.

DIAGNOSIS

The anomaly with which this paper is concerned is one of the group of anomalies associated with cyanosis and has no characteristic physical signs nor symptoms; however, the presence of situs inversus and cyanosis in a child should make one suspect that a congenital cardiac

anomaly exists, particularly transposition. Various murmurs associated with this anomaly have been described but none is pathognomonic. The murmurs probably originate from the defective septum which is usually present, rather than because congenital transposition exists. In approximately a third of the cases in which a stenosis of the pulmonic valve is a feature, a systolic murmur is heard over the second and third left intercostal spaces near the sternum. This murmur may be transmitted toward the left shoulder and is accompanied by a thrill. The murmur is often confused with that associated with a patent ductus arteriosus but the presence of cyanosis is a condition that favors making a diagnosis of stenosis of the pulmonic orifice. The electrocardiogram indicates the presence of right ventricular preponderance but again this is not characteristic of congenital transposition.

PROGNOSIS

The patients afflicted in the manner described here seldom live beyond childhood although rarely they have lived to middle age. The presence of an interventricular septal defect is associated with a slight increase of the life span, and is therefore an asset to these patients. The majority of patients, however, die within a few days or weeks after birth.

SUMMARY

In this study, five cases of transposition of the arterial trunks are presented (Table I). There are four cases of complete transposition according to the older classification of Rokitansky, and one case of partial transposition of the arterial trunks. Thus, according to Spit-

TABLE I

SUMMARY OF CASES

CASE	AGE AT DEATH	SEX	LESION	DUCTUS ARTERIOSUS	FORAMEN OVALE	INTERVENTRICULAR SEPTUM	MURMURS	ASSOCIATED ANOMALIES
1	20 days	Female	Complete transposition	Patent	Closed	Closed	None	None
2	18 days	Male	Complete transposition	Patent	Patent	Patent	Systolic	Situs inversus
3	3 months and 6 days	Male	Complete transposition	Patent	Patent	Closed	Basal systolic	None
4	1 month and 2 days	Male	Complete transposition	Patent	Patent	Closed	Apical systolic	None
5	7 months and 3 weeks	Male	Partial transposition	Closed	Patent	Patent	Basal systolic	Situs inversus

zer's more recent classification there are four cases of group III, representing a lack of torsion of the arterial trunks, and one case of group II, representing partial torsion.

The youngest patient was eighteen days of age and the oldest lived for seven months. In four of the five cases, the ductus arteriosus was patent but in one case it was represented by a mere fibrous cord and there was dimpling of the intimal surface of the pulmonary artery and aorta over the respective points of junction with the ductus arteriosus. In one case the foramen ovale was closed by a thin membrane, and it was but a slitlike opening in another case.

The interventricular septum was intact in three of the five cases and patent in two of them. The patency was attributable to an absence of the membranous portion of the septum. Systolic murmurs were audible in four of the five cases, but the patency of the fetal passages might well account for these murmurs. In two cases there was associated situs inversus. In four of the five cases the diagnosis of congenital heart disease was made without qualification before the patient died. The electrocardiogram indicated the presence of auriculoventricular dissociation in one case in which an interventricular septal defect existed.

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Department of Clinical Reports

LEFT AXIS DEVIATION IN DROPPED HEART*

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IT IS generally stated in the literature that the effect of habitus upon the electrocardiogram is such that a hypersthenic build tends to produce left axis deviation, whereas an asthenic build shows a tendency toward right axis deviation.[1, 2, 3] However, cardiac disease may so modify the electrocardiogram that the effect of habitus is overcome. We have recently seen two asthenic patients who presented no evidence of heart disease but in whom the electrocardiogram displayed definite left axis deviation. Our inability to find similar cases in the literature has prompted us to report this finding.

Both patients were young adults, one a female thirty years of age, and the other a male of twenty-five, who had essentially the same symptoms. They complained of palpitation, ease of fatigue, and anorexia. The present and past histories disclosed nothing etiologically significant in heart disease. The physical examination in both instances was entirely normal. Both patients were of the asthenic habitus. There were no abnormal cardiac findings on physical examination. Fluoroscopic examination of the chest revealed a markedly dropped type of heart. Electrocardiograms were taken as part of the routine examination (Fig. 1). A diagnosis of neurasthenia was made in both instances.

DISCUSSION

Left axis deviation is usually due to one of two factors, cardiac displacement or left ventricular hypertrophy. Elevation of the left leaf of the diaphragm, whether due to habitus, disease, respiration, or any increase of intra-abdominal pressure, may produce counterclockwise displacement of the heart with a tendency toward left axis deviation. Clockwise displacement has the opposite effect.[1] In our patients ptosis of the heart would be expected to produce the latter effect. This was not borne out by the electrocardiograms (Fig. 1). It is well known that any disease which will produce hypertrophy of the left ventricle and disturb the normal relationship between the muscle masses of the left and right ventricles will tend to produce left axis deviation. Such a factor could more than neutralize a tend-

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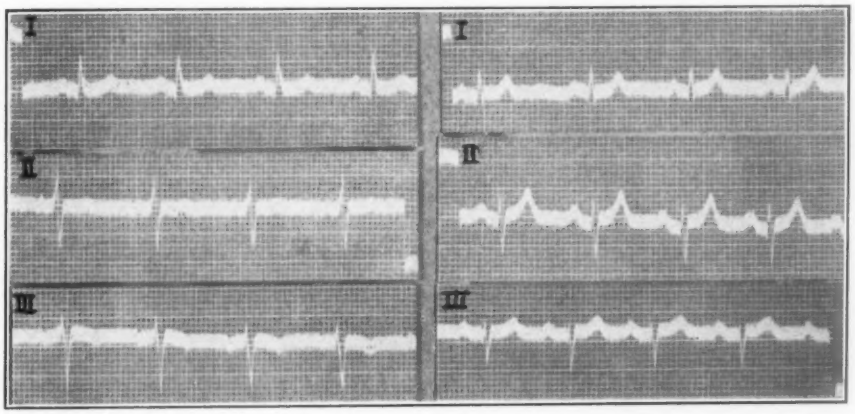
ency toward right axis deviation produced by ptosis. Our patients showed no evidence of left ventricular hypertrophy nor any etiological factor known to produce left ventricular strain. Since the above factors cannot explain the left axis deviation, an interpretation must be sought elsewhere.

There is adequate experimental evidence to indicate that at least two other factors may influence axis deviation. These are lateral shift of the entire heart and rotation of the heart on its longitudinal axis. Kountz and associates[4] have shown in revived human hearts that shifting of the heart to the right gave a left axis deviation, and shifting to the left, a right axis deviation. Fluoroscopic examination of both of our patients failed to reveal any evidence of lateral displacement of the heart.

If one views the teleoroentgenograms of an asthenic and a hypersthenic patient, it is clearly seen that the total muscle mass of the



A. *B.*

Fig. 1.—Electrocardiogram illustrating left axis deviation in a normal female (*A*) and male (*B*) of asthenic habitus with cardiac ptosis.

asthenic heart is farther to the right even though the right border is not displaced to the right. The muscle mass is also more caudad. Such displacement appears to be about a fixed point as a fulcrum at or near the base of the heart. If this fulcrum were fixed, the motion would be about a fixed point and the remarks already stated concerning clockwise and counterclockwise motion would hold. However, if the fulcrum were movable, at least to some extent, an effect of lateral shift of the entire heart might come into play. Obviously, in patients the predominant motion is of the former type. If it were in some instances of the latter type, an explanation of left axis deviation would be evident. We have no evidence to confirm or deny such a mechanism in our patients.

Ackerman and Katz[5] demonstrated a complete reversal of QRS in Leads I or III when the heart of the dog was rotated on its own longi-

tudinal axis. With the right ventricle anterior, left axis deviation was found; with the left ventricle anterior, right axis deviation. Such changes occurred with rotation as little as 50°. Motion of this type cannot be observed in the intact individual. It is hardly conceivable that the hearts of the asthenic and hypersthenic individuals differ only by position in one plane, or that the hearts of all asthenic or hypersthenic individuals rest upon the same longitudinal axis. Upon these bases, Nathanson[6] explained the inconsistency in the change in electrical axis with change in position of the body. One can readily see that right or left axis deviation may theoretically occur in patients with dropped hearts, depending upon the summation of the above factors.

SUMMARY

The occurrence of left axis deviation in a patient with dropped heart does not necessarily mean cardiac hypertrophy. The known effects of change in cardiac position upon the electrocardiogram can adequately explain such a finding.

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DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY HYPERTENSIVE AND CORONARY HEART DISEASE

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PAUL D WHITE, M.D., BOSTON, MASS.

DEXTROCARDIA with or without situs inversus is an uncommon but not a rare condition. Its association with hypertensive and coronary heart disease is, however, so unusual, particularly in its effect on the electrocardiogram, that we are presenting a case herewith.

A number of historical reviews have been published on the subject of dextrocardia itself. Of historical interest is the fact that Aristotle[1] observed transposition of viscera in animals. Fabricius[3] (1606) and Severinus[8] (1643) were apparently the first to describe dextrocardia in the human. Marie de Medici was one of two cases with this congenital anomaly reported by Riolanus[6] in the seventeenth century. Senac[7] (1749) was the first to classify dextrocardia into the acquired and the congenital types.

Since the early part of the nineteenth century important contributions have been made to the clinical recognition of isolated dextrocardia and dextrocardia with situs inversus (Küchenmeister,[4] 1824, and Bouillaud,[2] 1835). The first to employ roentgenography for the recognition of this condition was Vehsemeyer[9] (1897). Waller[10] (1889), who was the first to obtain a tracing of the action current of the human heart by means of the capillary electrometer, was also the first to obtain such tracings in two cases of dextrocardia with situs inversus. He showed that in such cases the usual Lead I is inverted and Leads II and III are transposed. This finding, in the absence of complicating heart disease, has been repeatedly confirmed since.

The clinical incidence of dextrocardia, presumably with situs inversus, was pointed out by Le Wald to be one in thirty-five thousand physical examinations of recruits for the United States Army. Still more infrequent is the association of dextrocardia with acquired functional or organic defects of the cardiovascular system. Willius[11] recently described dextrocardia with situs inversus and hypertension. The purpose of the present report is to record the hitherto undescribed association of dextrocardia with situs inversus, hypertension, and coronary disease.

CASE REPORT

C. H. W., a sixty-seven-year-old American unemployed chef, was first seen by us Sept. 26, 1937, because of a cold and a nonproductive cough of six days' duration. In 1927 he had had a nosebleed and at that time he was first told that he had high blood pressure; he has been treated for the hypertension ever since. He had passed

an insurance examination in 1922. In 1934 he began to have dyspnea on walking up one flight of stairs. In June, 1935, while working as a chef he lost consciousness for an undetermined length of time. On regaining consciousness, he had no paralysis. He was able to dress and go home unassisted. For several weeks following this experience, he was treated in bed for a "blood clot on the brain." He has had no recurring syncopal attacks. He began to suffer from sharp, penetrating pain over the left breast on effort or excitement soon after his syncopal attack in 1935. The pain is severe, lasts a few minutes, does not radiate, and is relieved quickly by nitroglycerine, grain 1/100. There has been no edema of the ankles or recent weight loss. His present weight is 168 pounds and his best weight has been 197 pounds. He has lost 30 pounds in two and a half years, without dieting. He uses tea, coffee, and tobacco in moderation, but no alcohol.

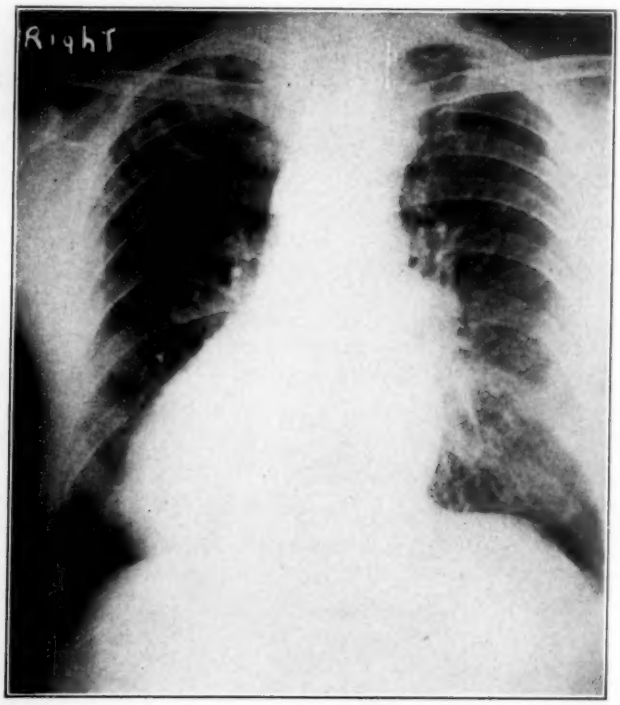

Fig. 1.—Teleroentgenogram demonstrating congenital dextrocardia with situs inversus, cardiac enlargement of the left ventricular type and increased density of the aorta, the knob of which is seen at the right of the upper sternum. The lung markings are increased. Note the gas below the diaphragm on the right and the high position of the left leaf of the diaphragm.

He has had mumps, pertussis, malaria in 1907, pleurisy in 1934, erysipelas in 1936, and pneumonia twice in 1936. There have been no operations or injuries. He was left handed in youth.

Family History.—Father died at fifty-two years, and mother at sixty-four years; the causes of their deaths are unknown. One brother was buried in a mine disaster. There is no history of consanguineous marriage.

Physical Examination.—The patient was a moderately well-developed and well-nourished sixty-seven-year-old white male, nervous, and not acutely ill. His temperature was 98.6° F. His pulse was regular at a rate of 72. The respiratory rate was 20. His blood pressure was 270 systolic and 130 diastolic. He weighed 168 pounds dressed.

Except for dental caries and an increased carotid pulsation, the examination of the head and neck showed nothing abnormal.

The chest was emphysematous, and tactile fremitus and pulmonary resonance were unimpaired over the lung fields. Below the right fifth rib anteriorly and over the right upper quadrant tympany was elicited; below the left fifth rib anteriorly and down the costal border dullness was present. The breath and voice sounds were normal; an occasional sibilant râle was heard anteriorly.

Heart.—The maximum apex impulse was found in the right fifth interspace in the anterior axillary line 11.5 cm. to the right of the midsternal line. The midclavicular

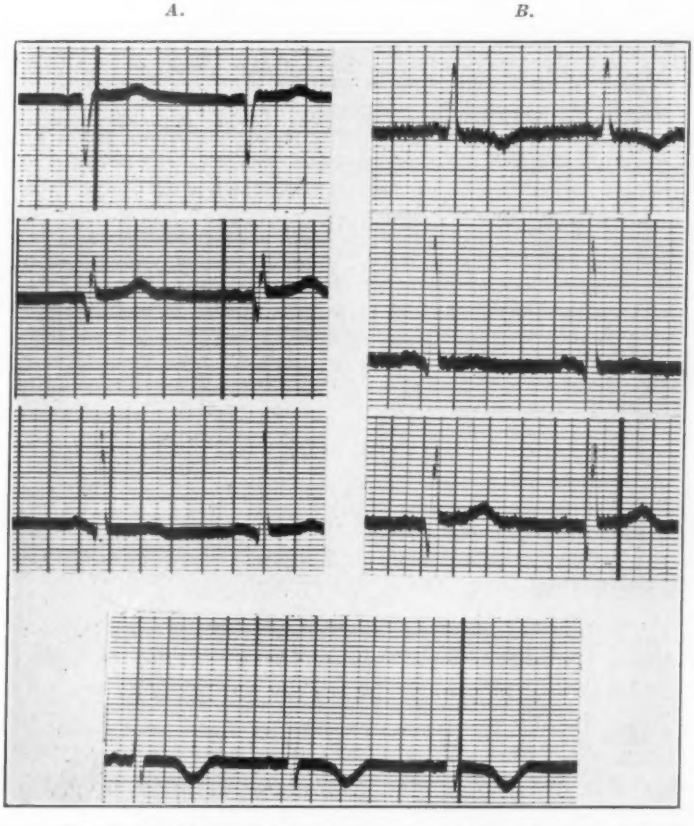

Fig. 2.—*A.* Electrocardiogram (Leads I, II, III, and IV*) showing normal rhythm, inverted P_3, marked right axis deviation (due to the combination of congenital dextrocardia and hypertensive heart disease), and changes due to coronary disease (upright T_1, prominent Q_2, high origin of T_2, low T_3, and inverted T_4. See text.
B. Electrocardiogram with Leads I, II, and III taken with a reversal of the arm wires—to "correct" for the dextrocardia.
Time interval equals 0.1 second, amplitude 1 mm. equals 0.1 millivolt.

*Lead IV taken according to the new method with exploring electrode at the cardiac apex, indifferent electrode on the right arm, and polarity so arranged that positivity is represented by upstrokes and negativity by downstrokes; the normal Lead IV has a diphasic QRS-wave with upright first phase (R) and an upright T.

line was 9 cm. to the right of the midsternum. The apex impulse was localized, forceful and regular. The left border of dullness was 4 cm. to the left of the midsternal line in the fourth interspace. There was no supracardiac dullness. There were no thrills. The heart sounds were distant over the left chest; over the right chest the heart sounds were loud at a regular rate of 72. The second sound in the

left second interspace* was greater than that in the right second interspace. A slight systolic murmur was heard at the apex. The pulses were full and equal. The blood pressure was 270 systolic, 130 diastolic, without alternation. Vigorous axillary and brachial pulsations were present.

The abdomen was flat; there was no tenderness or rigidity, and abdominal organs were not palpable. The right testicle was lower than the left.

Except for an irregular melanotic pigmentation and numerous varicosities, the extremities were normal.

The reflexes were active and equal.

Fluoroscopic Examination.—The heart was completely transposed, the mirror image of the usual position. The left border of the heart was blunt and rounded; the right border was sharp with a prominent apex visible in the right chest. The aorta was slightly increased in density and extended upward to the right. The retrocardiac space and aortic arch were visualized in the right anterior oblique view. The right leaf of the diaphragm was lower than the left; the stomach with its gas bubble was seen on the right; the liver was on the left. The lung fields and hilar shadows appeared normal; the diaphragmatic excursion was normal.

Teleroentgenographic Examination.—This was confirmatory of the fluoroscopic findings noted above (Fig. 1).

Electrocardiographic Examination.—Normal rhythm, ventricular rate 55. Inverted P-waves in Lead I, inverted QRS-waves in Lead I, marked right axis deviation, slight widening and notching of the QRS-waves in Leads II and III, prominent Q-waves in Lead II, upright T-waves in Lead I, high origin of the T-waves in Lead II, low T-waves in Lead III, late deep inversion of the T-waves in Lead IV (Fig. 2).

DISCUSSION

The recognition of dextrocardia with situs inversus in this case depended upon the physical examination, the visualization of the transposition of the heart, the stomach, and the liver by roentgen ray, and the inversion of the P-waves in Lead I of the electrocardiogram.

The presence of hypertensive heart disease was recognized by the elevated blood pressure and the enlargement of the heart on physical and x-ray examination, and was suggested by the unusually marked right axis deviation in the electrocardiogram in the presence of congenital dextrocardia.

The diagnosis of coronary heart disease was made upon the history of pain just to the left of the sternum caused by effort or excitement and relieved by nitroglycerin, and upon the unusual electrocardiogram.

The electrocardiogram is of particular interest and is apparently unique. In the uncomplicated case of congenital dextrocardia with the situs inversus the electrocardiogram shows merely total inversion of Lead I (P, QRS, and T) and transposition of Leads II and III. The unusual features of the present electrocardiogram are the marked amplitude of the inverted QRS in Lead I (due to the acquired heart disease superimposed on the dextrocardia), the *upright* T_1, which is to be interpreted as a "coronary T," the prominent Q_2 and high origin of T_2, which would ordinarily signify "Q_3T_3 coronary changes," the low T_3 having

*Actually the aortic area, because of the transposition.

the same significance as a low T_2 in the case of a heart normal in position, and a deeply inverted T_4 (Lead IV being taken in relation to the heart position exactly as in the normal person). The exact correlation of the electrocardiographic changes with damage or coronary insufficiency in any one or more areas in the heart muscle is difficult, as so often occurs in a chronic case. The changes in Leads I and II (the usual Lead III) suggest that both apical (or marginal) and basal areas are affected. The presence of R_4 tends to rule out the existence of a large apical scar.

SUMMARY

A case of a man, sixty-seven years old, is presented with congenital dextrocardia and situs inversus complicated by hypertensive and coronary heart disease. The electrocardiogram is of particular interest since it shows the effect of the various conditions cited. We have found no other such case recorded.

SUPPLEMENTARY NOTE.—Since the completion of our paper there has appeared an interesting case report by Crawford and Warren of a patient with congenital dextrocardia and situs inversus complicated by coronary thrombosis. The electrocardiogram, however, is quite different from ours for two reasons: In the first place, in their case the infarct was evidently situated at the base of the left ventricle with inversion of the T-waves in Leads II and III, and Lead I was normal; in the second place, there was no abnormal axis deviation after correction for the dextrocardia. Thus, both their case and ours are unique.
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AN UNUSUAL P-WAVE IN LEAD IV*

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CHICAGO, ILL.

RECENTLY, an unusual contour of the P-wave was encountered in Lead IV, which was considered to indicate a shift of the heart's position to the left with an approximation of the right auricle to the chest wall in the neighborhood of the precordial electrode in the fourth interspace to the left of the sternum. This interpretation was confirmed by the roentgenogram. It is felt that this peculiar P-wave is of sufficient interest to merit the reporting of the case in which it was found.

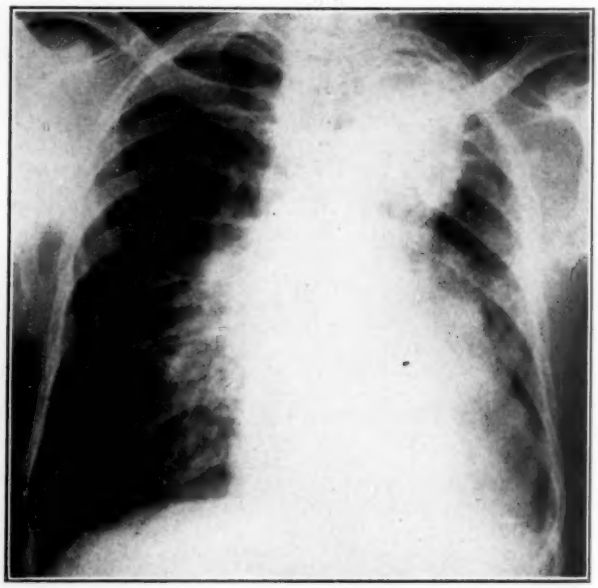

Fig. 1.

CASE REPORT

M. F., a colored male, aged sixty-five, was admitted on Dr. W. Buchbinder's service, complaining for two months of shortness of breath, cough and swelling of the ankles. The cough was productive and the patient was orthopneic. There was slight clubbing and cyanosis of the fingertips. The neck veins were distended and the patient was edematous. There was limitation of respiratory motion of the left upper chest with impairment of resonance in this area. There were coarse, moist râles at the base of both lungs. The heart was moderately enlarged to the left and the basal dullness was widened. A systolic murmur and a protodiastolic gallop were heard over the base of the heart. The blood pressure was 190/130 and the blood Wassermann reaction was negative.

*From the Cardiovascular Department, Michael Reese Hospital.

An x-ray plate was taken while the patient was in the hospital (Fig. 1) and showed a cardiothoracic ratio of 15.7/27.3. There was prominence of both the left ventricular and pulmonary bows. The aorta was of the short squat type. Calcified deposits were present in both axillae and cervical regions. The entire upper lung field from the second rib anteriorly up to the apex was densely clouded and contained large plaques of calcified deposits. On fluoroscopy, these plaques were found to be in the posterior half of the lung field. There was retraction of the trachea and superior mediastinum toward the lesion in the left upper lung field. This roentgenogram was interpreted as being indicative of old tuberculosis, with calcareous deposits in the left upper lung field and traction on the heart by this lesion. The heart itself was considered to be abnormal.

The clinical diagnosis was arteriosclerotic heart disease, hypertension with marked enlargement of the left ventricle, and congestive heart failure. After a short stay, the patient left the hospital improved in health.

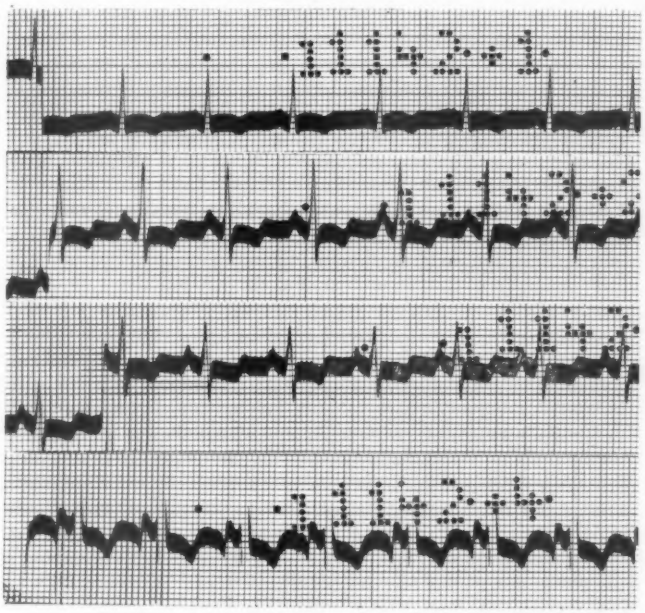

Fig. 2.

COMMENT

The electrocardiogram (Fig. 2) taken on Nov. 2, 1936, was interpreted as indicating an abnormal heart. On the basis of P_4, and without knowledge of the other findings of the patient, this was interpreted as follows: The diphasic P_4 looks like a P-wave which is recorded over the auricle and hence would suggest that the heart is displaced to the left. The P-wave in Fig. 2 resembles the P-wave usually obtained when the precordial electrode is placed over the second or third interspace in the right parasternal line and also resembles in contour the type of wave reported by Wilson, Macleod, and Barker,[1] among others, when an electrode directly on the exposed auricle is paired with an indifferent electrode at a distance.

With the precordial electrode placed in the fourth interspace to the left of the sternum, a P-wave such as this has not been seen in any other of the more than 3,000 records taken at the Heart Station. It was considered that such a P-wave should therefore indicate that the auricle in this patient had been shifted so as to lie close to the region where the precordial electrode was located, hence it would follow that the heart had been displaced to the left. This surmise was verified by the roentgenogram, which showed that the heart had been pulled over toward the left. This case serves to emphasize the importance of the heart's position in determining the character of the electrocardiogram obtained with precordial electrodes.

SUMMARY

A case is presented showing an unusual P-wave in the fourth lead, when the precordial electrode is in the fourth interspace to the left of the sternum. This consisted of a diphasic P-wave with sharp transition between the two phases, resembling the type of wave seen when a unipolar lead is employed with one electrode directly over the auricle. In this case the abnormal P was associated with a displacement of the heart to the left caused by traction which resulted in placing the right auricle beneath the area of the precordial electrode.

I wish to acknowledge my indebtedness to Dr. Louis N. Katz, who first suggested the interpretation of the electrocardiogram, for his guidance in preparing this report.

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TWO-TO-ONE AND THREE-TO-ONE LEFT BUNDLE-BRANCH BLOCK IN THE PRESENCE OF AURICULAR FLUTTER

Case Report*

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ELECTROCARDIOGRAMS revealing ventricular responses that alternately show bundle-branch block and normal intraventricular conduction in the presence of normal sinus rhythm and normal P-R intervals are distinctly rare. Reported instances include those of Leinbach and White[1] and Kelly.[2] Cases in which ventricular complexes of normal duration appear with varying frequency in the presence of bundle-branch block are somewhat more common.[3-9] Robinson[10] has reported an instance of alternating normal intraventricular conduction and bundle-branch block in the presence of complete heart-block, and White and Stevens[11] have recorded the appearance of transient bundle-branch block during a paroxysm of rapid auricular flutter. However, we have not encountered in the literature or in the electrocardiograms of over 11,000 patients on file at the Rhode Island Hospital, the combination presented by the case herein reported.

CASE REPORT

G. M., a sixty-five-year-old, unmarried salesman, was first seen by Dr. Alex M. Burgess on Aug. 12, 1936, complaining of recurrent lightheadedness and faintness.

A year and a half before, he had experienced some indefinite chest pain, at which time his physician told him he had a "heart attack" and kept him in bed for one week. Digitalis had been taken since, sporadically. While there had been mild shortness of breath on stairs, there had at no time been any edema, cough, or palpitation.

He stated that after lifting a heavy box nine days previously, he had felt suddenly weak and faint—a symptom occasionally noticed on exertion for the past year and a half. There was no pain or dyspnea with this attack. The family history and past history were noncontributory. Physical examination by Dr. Burgess included the following findings. The blood pressure was 152/84. The heart rate was 84 beats per minute, with an irregular rhythm. No murmurs were heard, and there was no apparent enlargement. The lungs were clear, and there was no edema. Moderate sclerosis of the retinal and peripheral arteries was present.

Eleven days after his first visit to Dr. Burgess, he became dizzy and noticed dimness of vision while climbing stairs after a hard day. He perspired freely, felt some oppression in his chest, and was apprehensive. The next morning his physician found the blood pressure to be 190/110. The heart rate was 90, and the rhythm still irregular. He was advised to enter the Rhode Island Hospital for further study.

He was admitted to the hospital on the same day, twelve days after he had first been seen, and appeared comfortable and lay flat in bed without distress. Examination revealed the same findings as before, except that the blood pressure had fallen to 150/82. There was no fever.

*From the Heart Station of the Rhode Island Hospital, Providence, R. I., under the direction of Dr. Frank T. Fulton.

Laboratory data, including a Wassermann test, blood count, urine examination, and blood chemistry, provided no significantly abnormal findings.

Orthofluoroscopy revealed a prominent aortic arch and clear lung fields. The total transverse diameter of the heart was 13.4 cm., and the internal thoracic diameter measured 23.4 cm.

The patient was fully digitalized and was discharged on Sept. 9, 1936, after an uneventful stay. Since then he has been active and generally well. There is still occasional faintness. He has continued to take one pill of digitalis (0.1 gm.) daily.

DISCUSSION

In Fig. 1, Lead I, it is apparent that the ventricular rate is perfectly regular, and that every second beat reveals left bundle-branch block (new terminology). In Lead II the same condition prevails except in

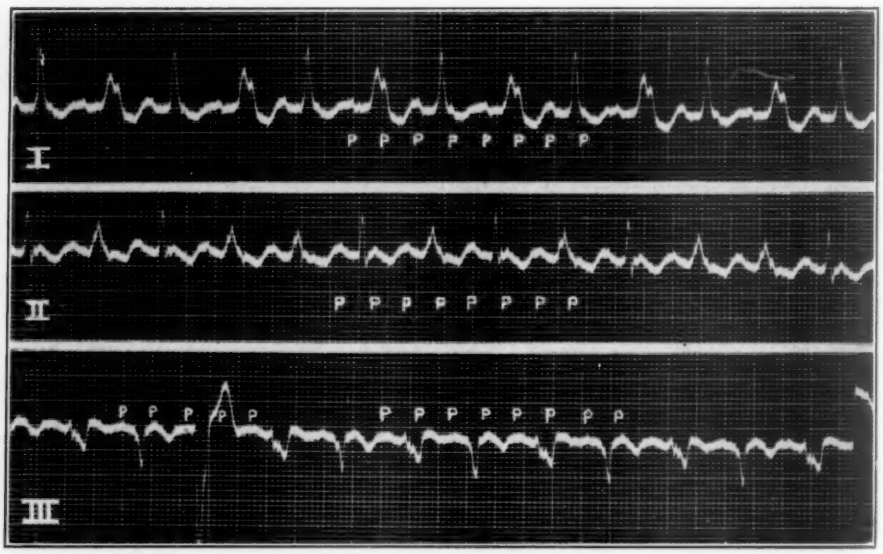

Fig. 1.—The three standard leads taken Aug. 14, 1936. The ventricular rate is 127, and the auricular rate 254 per minute (auricular flutter with 2:1 block). Through most of the tracing every second ventricular beat shows left bundle-branch block (2:1 and occasionally 3:1 left bundle-branch block). The normal ventricular response measures 0.08 sec.; the widened ventricular beats measure 0.14 sec. One ventricular extrasystole is present in Lead III.

two places, where two beats showing bundle-branch block occur in succession. In Lead III the rate is regular except for one ventricular extrasystole, and normal beats and those showing bundle-branch block alternate. Throughout the tracing the interval between ventricular beats approximates 0.46 sec. Between the ventricular extrasystole and the preceding beat, the interval is 0.41 sec., and between it and the following beat the interval is 0.52 sec. The early occurrence of this beat is evidence of its identity as a ventricular extrasystole rather than as an aberrant ventricular response from a normally conducted auricular impulse.

How long the unusual condition shown in Fig. 1 endured we do not know, as the next available tracing was taken eleven days later (Fig.

2*A*). At that time the ventricular rate had slowed, and the record presents the ordinary appearance of auricular flutter, with the ventricular rate controlled by digitalis. Following this, seven tracings were taken at intervals through Dec. 4, 1936. All of these were very similar to that shown in Fig. 2*A*. The flutter persisted with a constant auricular rate, the ventricular rate varying between 42 and 82 beats a minute. Bundle-branch block did not recur, and the QRS complex always measured between 0.08 and 0.09 sec. On Aug. 27, 1936, carotid sinus pressure was tried and increased the block to 8:1 but did not alter the appearance of the ventricular complex.

The final tracing, Fig. 2*B*, was taken fourteen months after that shown in Fig. 1. At this time normal sinus rhythm prevailed, with frequent ventricular extrasystoles. The normally conducted ventricular responses

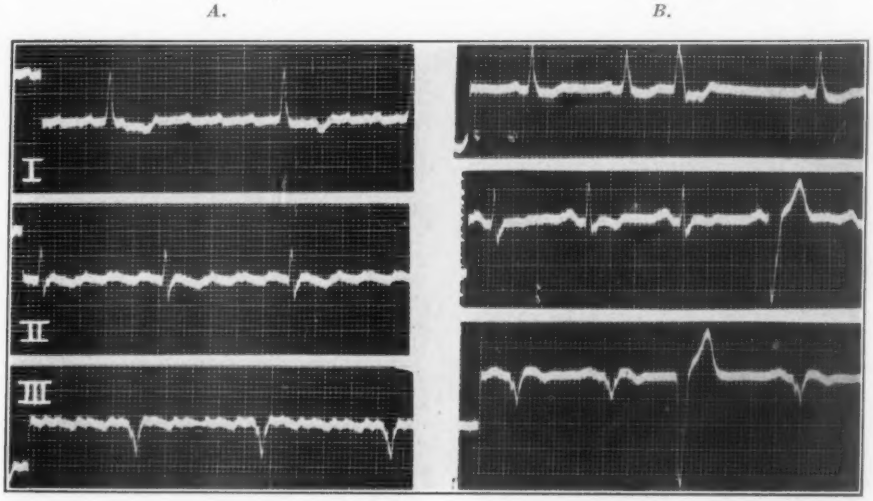

Fig. 2.—*A*, The three standard leads taken Aug. 25, 1936. Auricular flutter persists. The A-V block has been increased following digitalis administration to 4:1 and 6:1. The ventricular rate is 54 per minute. The bundle-branch block has disappeared, the QRS complexes measuring 0.08-0.09 sec.

B, The three standard leads taken Oct. 14, 1937. The auricular flutter has reverted to normal sinus rhythm with frequent ventricular extrasystoles. The conducted ventricular responses are slightly wider, measuring 0.08-0.10 sec. Bundle-branch block is absent.

show slight widening, but bundle-branch block is absent. A tracing in the fourth lead taken at this time, but not reproduced in Fig. 2*B*, revealed a large Q-wave and a normally inverted T-wave.

In the light of the clinical observations on our patient and the evidence contained in references cited at the beginning of this paper, we believe that the abnormality of ventricular beat shown in Fig. 1 resulted from the rapid ventricular rate in the presence of significant disease of the coronary arteries. It is possible that the conduction defect in the left bundle was associated with thrombosis of one or more of the small vessels supplying this area. We rather expect the bundle-branch block to recur eventually, but we have not observed its reappearance in fourteen months.

SUMMARY

A case is reported illustrating the unique combination of auricular flutter and 2:1 and 3:1 left bundle-branch block. Subsequent tracings covering a period of fourteen months are described, and the probable etiologic factors in the original electrocardiographic abnormality are suggested.

We wish to express our indebtedness to Dr. Alex M. Burgess, who took and made available to us the tracing reproduced in Fig. 1, and provided the original clinical observations on this patient.

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Department of Reviews and Abstracts

Selected Abstracts

Page, Irvine H., and Sweet, J. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs With Experimental Hypertension. Am. J. Physiol. 120: 238, 1937.

Hypertension of the order of 240/160 mm. Hg was produced in dogs by constricting the renal arteries of dogs by means of Goldblatt's clamp. It was maintained for several months. Hypophysectomy in these animals reduced the arterial pressure to levels slightly above normal (150/100) or below normal (90/40) within a period of twenty days. Hypophysectomy in normal dogs reduced the arterial pressure only slightly (from about 140/170 to 116/50).

Increasing the constriction of the renal arteries after hypophysectomy again produced a rise in blood pressure, but this tended to be less marked and transient, especially in the dogs which became sluggish and fat and exhibited reduced basal metabolism and often diabetes insipidus. The rise was better maintained in dogs which were thin and active and with normal or elevated basal metabolism.

After hypertension had been reduced by hypophysectomy, feeding thyroid (0.8 gm.) raised the blood pressure moderately (190/120), and injection of theelin (1 c.c. daily) or antuitrin-S (1 c.c. daily) had no effect.

The effect of hypophysectomy on hypertensive dogs is believed to be an indirect one. It is postulated that the responsiveness of the blood vessels to chemical stimuli from the kidneys with constricted renal arteries is reduced. This may be due to lack of the secretions which may in turn be due to withdrawal by hypophysectomy of the chemical stimuli normally afforded them by the hypophysis.

AUTHOR.

Malméjac, J., and Desanti, E.: Concerning the Cardiovascular Properties of Hypophyseal Extract. Compt. rend. Soc. de biol. 125: 475, 1937.

Watery extract of the hypophysis (Carrion Co.) was injected intravenously into dogs anesthetized with chloralose and was found to give rise to a sharp fall in arterial pressure accompanied by dilatation of peripheral vessels (plethysmographic measurements) in kidney and foot. The surprising result was that the spleen, in contradistinction to the behavior of other organs, contracted sharply.

STEELE.

Scheiner, H.: Hypertensive Action of an Ultrafiltration Extract of Dog Spleen Previously Treated With Posterior Pituitary Extract. Compt. rend. Soc. de biol. 125: 125, 1937.

An extract of spleen, obtained from the fresh organ after a period of electrical stimulation of its nerve by ultrafiltration, has been previously studied by the author, and it was shown to cause usually a fall in arterial pressure, but in a certain number of instances (8 out of 22) was followed by a rise. He has also shown that

when the animal has been previously cocainized and atropinized, injection of the spleen extract was regularly followed by a rise in arterial pressure. In the present series of experiments the extract of spleen was given to dogs under chloralose anesthesia after they had been treated with an extract of the posterior pituitary gland. Just as after cocaine and atropin the splenic extract now gave rise regularly to a rise in pressure. One important difference was noted; whereas injection of cocaine and atropin had to be repeated after an interval of one hour to maintain the pressor effect of the splenic extract, the effect of posterior pituitary extract lasted for at least four or five hours. Scheiner believes the extract of the hypophysis —it is soluble in 80 per cent and insoluble in 95 per cent alcohol and insoluble in acetone—to be similar to, if not identical with, vasopressin.

STEELE.

Dicker, E.: An Autolyzing Kidney Gives Rise to Substances Which Produce Hypertension. Compt. rend. Soc. de biol. **126:** 88, 1937.

Both renal arteries of dogs were completely clamped. Twenty-four hours later the animals were anesthetized by chloralose, and arterial pressure in the femoral artery was recorded while releasing the clamps, first on the one, and then the other side. Arterial pressure rose 40 to 50 mm. Hg and remained elevated for about twenty minutes after release of each artery.

If instead of opening the clamps the kidney was perfused with Locke's solution and the perfusate injected into the *femoral* vein, a similar rise occurred. The rise in pressure failed to occur if the perfusate was injected into a *mesenteric* vein.

The vasopressor principles of the autolyzing kidney survive prolonged boiling, oxidation with potassium permanganate, and aging; they are soluble in alcohol but not in ether.

STEELE.

Bärtschi, W.: The Reaction of the Coronary Arteries to Histamin. Arch. f. d. ges. Physiol. **238:** 606, 1937.

The reaction to histamin of excised arterial rings from twenty-seven steers was found without exception to be contraction. The threshold dose was from 1 part in 2½ millions to 1 part in 500,000. He demonstrates a "cumulative" action of the drug in that repetition of a dose which failed to give rise to contraction succeeds in doing so after an interval of thirty minutes. Acetylcholin is effective in contracting the coronary arteries in approximately 1/10 the dose of histamin, but no "potentiation" of the one drug by the other was demonstrable.

STEELE.

McGuire, Johnson, Hauenstein, Virgil, and Shore, Rose: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method. Arch. Int. Med. **60:** 1034, 1937.

The cardiac output has been determined by the direct method of Fick and the modified acetylene method of Grollman for six patients with serious heart disease. In all the patients the cardiac output was subnormal.

The results demonstrated close qualitative comparison between the modified acetylene and the direct method, although the absolute values tended to be lower by the acetylene method.

No relationship between the severity of symptoms or the severity of failure, as judged by measurements of circulatory efficiency, and the level of cardiac output was demonstrated.

AUTHOR.

Van Liere, Edward J., and Sleeth, Clark K.: Immediate Effect of Tincture of Digitalis on Emptying Time of Human Stomach. Arch. Int. Med. **61**: 83, 1938.

It was found that 5 c.c. of tincture of digitalis when mixed with a standard test meal (consisting principally of 15 gm. of farina) decreased the normal emptying time of the stomach on an average of 18.5 per cent in seven healthy young men. The results all lay in the same direction, and there were no exceptions. In no case was the decrease in the emptying time less than 12.9 per cent, and the greatest decrease noted was 24.6 per cent.

The conclusions which may be drawn from the work reported here are as follows: Tincture of digitalis administered in doses of 5 c.c. is capable of decreasing the emptying time of the stomach of the average person about 18 per cent, as based on experiments performed on seven subjects. It may thus be given immediately before or directly after a meal without any deleterious effect on gastric motility. Experimental evidence is offered which throws light on the causation of the diarrhea which often accompanies the administration of digitalis. Finally, since digitalis is often given in conditions associated with anoxemia, which has been shown to inhibit gastric motility, the fact that it is capable of decreasing the emptying time of the stomach is of practical importance.

AUTHOR.

Hubensack, E.: The Alteration of the Electrocardiogram in the Course of Diphtheria. Ztschr. f. Kreislaufforsch. **29**: 434, 1937.

A study based on 620 proved cases was made. Not all electrocardiographic abnormalities in diphtheria are associated with clinical manifestations of heart damage. When the electrocardiogram is abnormal, tachycardia is usually present and persists as long as the electrocardiogram remains abnormal. Conduction disturbances of any variety can occur. The mortality is high in those cases with total heart block and slow ventricular rate. Patients with other types of electrocardiographic abnormalities tend to recover. There is need of long-continued follow-up studies to determine whether in recovered patients any residue of heart damage remains.

KATZ.

Wollheim, E.: A New Depressor Substance Elaborated by the Body and Its Meaning for Essential Hypertension. Acta med. Scandinav. **91**: 1, 1937.

The present report describes studies conducted upon the thermostable vasodepressor obtained from normal urine, since the time it was first described by Wollheim and K. Lange in 1932. Urines from 225 normal and 102 hypertensive individuals have now been studied, each on at least five or ten separate occasions. Tests for depressor effect were carried out on rabbits.

The substance was found to be present in normal human urine, except rarely in an occasional sample, and in the urine of horses. It is absent from the urine of individuals suffering from essential hypertension or present only in small amounts in less than 8 per cent. In acute and chronic nephritis the material is present in the usual amounts, and the urine of pregnant women is rich in it. A substance quite similar in chemical and pharmacologic properties can be obtained also from the posterior lobe of the pituitary gland.

This thermostable substance, labelled by the author "depressan," can be distinguished from all of the previously described depressor substances found in the urine by its behavior on boiling with acid and alkali, by its peculiarities toward the usual dissolving and precipitating agents, by use of dialysis and electrodialysis. One liter of urine yields from 0.2 to 0.5 gm. of dry substance.

The physiologic activity of the substance either from the pituitary gland or from the urine depends upon dilatation of the peripheral vessels of from 20 to 50 per cent as measured by rate of perfusion of the rabbit's ear. The author states that the widening of the vessels is independent of the nerve supply. Reaction of heart, respiration, or intestinal muscle was not observed.

The duration of the depressant action is relatively long, depending, as does the extent of fall in blood pressure, upon the dose. In atropinized rabbits 1 mg. intravenously was followed by a fall of 20 mm. Hg for five to ten minutes and 40 mg. by a fall of 50-70 mm. Hg for one to two hours. The duration of its action is another point in differentiation from other substances.

The intramuscular injection of the substance into 18 patients with hypertension resulted in a fall of blood pressure in 14, beginning six to twelve hours after injection and lasting for from one to three days. The systolic pressure fell 30-50 mm. Hg, the diastolic about 20. The dose used was 1 c.c. (if the solution was made up according to that used for tests in rabbits, the amount of dry substance should have been roughly 100 mg.). Four patients failed to respond. Two of these were instances of severe nephrosclerosis. There is no mention of having administered the substance to normal individuals. The author believes that essential hypertension is called into being through a lack of "depressan."

STEELE.

Schellong, F., Heller, S., and Schwingel, E.: The Vector Diagram—A New Method of Studying the Heart. I. Ztschr. f. Kreislaufforsch. **29:** 497, 1937.

The authors describe a method utilizing two cathode ray tubes connected to three leads, in such a way that one cathode ray tube depicts, as a standing wave on the fluorescent screen, the spatial distribution of the vector of the electrical axis on the frontal plane and the other the vector of the electrical axis in the sagittal plane of the body. These are called the vector diagrams of the heart. These permit one to reconstruct the spacial distribution of the changes in the electrical axis of the heart during a heart cycle, either in two or three dimensions. Since it records something different from the electrocardiorgam, the vector diagram will not displace but will supplement the electrocardiogram and will be found, so the authors believe, clinically useful when developed on an empirical basis. Changes in contour of the vector diagram may be found of value in differentiating various cardiac conditions.

KATZ.

Schellong, F., and Schwingel, E.: The Vector Diagram: II. Meaning of Slurring and Splintering. Ztschr. f. Kreislaufforsch. **29:** 596, 1937.

The vector diagram recorded spatially or stereoscopically shows that some instances of slurring and notching are benign and due merely to a change in the position of the heart, while others are found to indicate disturbances in the spread of the impulse.

KATZ.

Otto, H.: Myocardial Involvement in Tonsillitis. Ztschr. f. Kreislaufforsch. **29:** 471, 1937.

The damage to the heart in tonsillitis is sometimes demonstrable in the electrocardiogram, as a prolongation of P-R and QRS intervals, as S-T depression, as flattening or inversion of T, as a split P, as a Q_3, as low "voltage" or as more advanced A-V block. Such evidence was found in 63 per cent of 336 cases studied. Tonsillectomy tended to decrease the electrocardiographic abnormalities.

KATZ.

Misao, T., Maéda, N., Tanaka, T., Noma, K., and Itoh, S.: The Electrocardiogram in Agonal States of Man. Ztschr. f. klin. Med. **130:** 332, 1936.

In the agonal state, P-R, QRST, and QRS durations increase. This occurs despite acceleration of the heart. The S-T becomes depressed, and the arrhythmias in this state are variable. Most commonly sinus standstill is found, followed by idioventricular rhythm, ventricular standstill, or ventricular fibrillation. Fibrillation may be temporary, the idioventricular rhythm being restored and standstill occurring terminally. In other cases, the sinus rhythm persists and A-V block occurs. Rarely, the normal mechanism persists until standstill. Extrasystoles and auricular extrasystoles are rare.

KATZ.

MacMahon, H. Edward: Hypertrophy of the Heart in Infants. Am. J. Dis. Child. **55:** 93, 1938.

A review of the types of cardiac hypertrophy in infants clearly shows that many different factors may play important etiologic rôles. Furthermore, when considered from a structural standpoint, the histologic picture is likewise variable. One change has been almost universally emphasized, namely, an increase in the size of the individual muscle fibers, whether in true hypertrophy or in a mere pseudohypertrophy resulting from the storage of glycogen. The purpose of this brief report is to point out that in cardiac hypertrophy appearing at an early age, in addition to the increase in size of the muscle fibers, there may be a true proliferation of these elements. A corollary to this is the suggestion that since proliferation of the fibers of the cardiac muscle may occur in hypertrophies of this group, it is possible that during the same period myocardial regeneration following severe injury may likewise occur.

AUTHOR.

Gloyne, S. R., and Shiskin, Cecilia: Mitral Stenosis and Pulmonary Tuberculosis. Tubercle **18:** 394, 1937.

Mitral stenosis and pulmonary tuberculosis in autopsy records of Victoria Park for the last sixteen years contain 121 cases of mitral stenosis in only one of which pulmonary tuberculosis also occurred. From this and other records quoted, the following deductions may be made:

1. Cases of mitral stenosis rarely exhibit active lesions of pulmonary tuberculosis.

2. There were no cases showing old fibrotic or healed lesions of pulmonary tuberculosis.

Three pathologic explanations of the infrequency of this combination of diseases may be suggested:

1. That there is a true cellular and humoral immunity against tuberculosis, due to an excess of blood in the pulmonary circulation which may increase phagocytosis and even neutralize the products of bacterial metabolism. A similar hypothesis has been made to explain the beneficent effect of artificial pneumothorax. Tileson also suggested that there was a "rheumatic diathesis" in mitral stenosis which was inimical to tuberculosis.

2. That pulmonary congestion results in pulmonary fibrosis which protects against tuberculosis.

3. That there is an alteration in the hemorespiratory exchange. Of these numerous changes, oxygen desaturation, increased carbon dioxide arterial tension, and deviations in pH value of the blood have all been cited. One of the authors

(C. S.) recently investigated this point in connection with a research on the pH values of venous blood in cardiovascular and respiratory disease. The results obtained in mitral stenosis are given.

MONTGOMERY.

Howard, John Eager, and Barker, W. Halsey: Paroxysmal Hypertension and Other Clinical Manifestations Associated With Benign Chromaffin Cell Tumors (Phaeochromocytomata). Bull. Johns Hopkins Hosp. **61**: 371, 1937.

From this study of proved cases, we feel that a fairly definite clinical picture emerges by which may be evaluated the possibility or probability of the presence of a pheochromocytoma in a suspected patient. The individual most likely to have a pheochromocytoma will be one who is youthful or in early middle age, of either sex, and in good health. The attacks of hypertension may vary widely in duration from a few minutes to many hours. There will generally be no known predisposing cause initiating the attacks, although the assumption of certain positions sometimes has been observed to induce attacks, and exertion and emotional stress have been felt by some patients to be precipitating factors. The attacks are more likely to come after retiring at night, and especially in the early morning hours. The patient will probably look and feel perfectly well when not actually having an episode of hypertension, although persistent hypertension is too common in this group to be totally ignored as part of the syndrome. Should persistent hypertension exist, the same manifestations will be found in the retinal arteries, heart examination, and urinalysis as are commonly seen in patients suffering with so-called essential hypertension. Electrocardiographic findings will be of no help in the differential diagnosis, even during a hypertensive attack. A mass in the abdomen, on the side of the tumor, may or may not be palpable on physical examination; there is greater possibility of its being found either by flat x-ray plates of the abdomen or by pyelographic studies, but the correctness of the diagnosis should not be seriously questioned if no mass is detected by any of these means. After paroxysms of hypertension, albumin or sugar, or both, may possibly appear in the urine. Nothing in the way of medication has been found to influence materially the frequency, duration, or severity of the attacks. If tests are made with epinephrine or pituitrin, there will probably be found no hypersensitivity nor hyposensitivity. During the early part of an attack (associated with the rise in blood pressure) the patient will almost certainly become cold, pale, or mottled, and complain of palpitation. Quite pronounced nausea and probably vomiting are almost certain to be present and, if of long duration, especially if accompanied by hyperventilation, may lead to tetany. Very severe headache is more likely than not to be complained of. If the attack is severe or prolonged, signs of cardiac incompetence are to be looked for, such as pulmonary edema, sudden hepatic enlargement, or distended neck veins. Precordial pain with radiation to the neck, down the arms, or other areas characteristic of stenocardiac attacks is quite likely to be present. Very pronounced sweating is likely to occur either during or just after the severe episode has passed. Even without any of the symptoms listed above, the patient whose usual resting blood pressure is normal may at any time be found to have quite marked temporary hypertension. In other words, milder paroxysms of hypertension may occur without the patient's being aware of them at all, just as is observed so frequently in the early stages of so-called essential hypertension. It is perhaps worthy of emphasis, however, that in patients suffering from essential hypertension the course may be totally asymptomatic for a long period of time, whereas in this group of patients the symptoms are of sufficient severity early in the course of the disease to bring the patient to the doctor.

AUTHOR.

Longcope, Warfield T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension. Ann. of Int. Med. **11**: 149, 1937.

A study of twenty-two cases of chronic bilateral pyelonephritis indicates that a number of complications and accessory facts may modify the usual course of this disease. As the disease advances, it is usual to find that the blood pressure rises. In ten of the fifteen patients observed during the terminal or advanced stages of the disease, the blood pressure was above 160 mm. systolic and 105 mm. diastolic. In seven cases, observed during the early stages of the disease, only one had a systolic blood pressure of over 140 mm., or diastolic pressure of over 85 mm. The hypertension was not associated with pronounced or excessive arteriolosclerosis in nine fatal cases. In three of the fatal cases, the pyelonephritis was associated with a chronic diffuse glomerulonephritis. The development of the ophthalmologic picture of retinal arteriolosclerosis and retinitis is more related to the development of the hypertension than to the presence or degree of renal insufficiency. When chronic renal insufficiency does occur, it is often associated with intermittent or persistent hypertension. The explanation for the hypertension which occurs during the later stages of pyelonephritis is not clear. The bacterium which is usually responsible for the infection in the *Bacillus coli*.

HINES.

Clerc, A., and Sterne, J.: A Case of Repeated Anginal Crises With Paroxysmal Hypertension and Vasomotor Disturbances: A Record of Medical Treatment, Two Surgical Interventions, and of the Efficiency of a Synthetic Sympathicolytic Drug. Bull. et mém. Soc. méd. d. hôp. d. Paris **53**: 562, 1937.

A woman, 60 years old, essentially normal as to physical and laboratory examination except for arterial blood pressure of 160 to 180 mm. Hg systolic, complained of attacks of severe pain in the heart of fifteen months' duration. The attacks of "anginal crises" were observed (she was hospitalized on Oct. 3, 1934) to occur in the following manner: First, an abrupt rise in the systolic level of pressure to 220 to 240, once to 300; immediately thereafter an intense scarlet blush over face, chest, and arms, leaving the rest of the body pale; then constriction of the chest, severe precordial pain radiating to the shoulders, left arm and hand, occasionally to the right. The patient cried out with pain and pressed both hands to her chest. The attacks passed off in twenty minutes or so, recurred usually about three times in twenty-four hours, and were unaccompanied by change in heart rate or electrocardiographic disturbance. After failure of every conceivable drug—a list being given—to relieve the attacks, left stellate ganglionectomy was performed on Dec. 5, 1935, without relief for more than a few hours in spite of development of Horner's syndrome, and on March 21, 1936, the right ganglion was removed with relief for about ten days. Innumerable drugs were again tried including one preparation of Fourneau and Beret, piperidinomethyl-benzo-dioxan, without relief. A second synthetic benzo-dioxan (diethylaminomethyl-benzo-dioxan) afforded immediate relief and after a short while almost complete disappearance of the attacks. The dose was 0.20 gm. a day in four doses, by mouth. Omission of the drug for about three days on two occasions was followed by return of the attacks. The remarkable point is that all three symptoms, pain, blushing, and paroxysmal hypertension, disappeared.

STEELE.

Clark, Eugene, and Kaplan, Bernard I: Endocardial, Arterial, and Other Mesenchymal Alterations Associated With Serum Disease in Man. Arch. Path. **24**: 458, 1937.

Two patients who had received large doses of antipneumococcus serum died after having typical symptoms of serum sickness, one of heart failure, the other of exten-

sion to another lobe and of hemorrhage. In both cases at autopsy inflammatory arterial and periarterial lesions were found. The structural alterations in these cases consisted of proliferation of histiocytes in the neural and valvular endocardium and in the intima of the aorta and the pulmonary interstitial mesenchymal tissue of the myocardium and other viscera. Necrotizing arteritis and periarteritis of the smaller coronary arteries formed a prominent finding in one case. It is felt that the composite picture presented by these two cases is incompatible with any disease hitherto described and that they are related to the administration of foreign serum.

MONTGOMERY.

Karsner, Howard T.: Primary Inflammation of Arteries. Ann. Int. Med. **11**: 164, 1937.

In addition to secondary inflammation of arteries due to extension of local inflammation or direct invasion, there is an inflammation which can be appropriately described as a primary arteritis. The causes of this form of arteritis are unknown or are ill-defined. The lesions found in primary arteritis have been classified and consist both of acute and chronic varieties. The chronic form is characterized by distribution of fibrosis in the three coats of the arteries and by delayed or absent secondary changes in the fibrous tissue. An improved nomenclature for the various types of arteritis would aid in correlating descriptive morphologic and clinical data so that the disease may be better understood.

HINES.

Bordley, James, III, Grow, Max H., and Sherman, William B.: Intermittent Blood Flow in the Capillaries of Human Skin. Bull. Johns Hopkins Hosp. **62**: 1, 1938.

The flow of blood in the minute vessels of the skin of the human leg may be clearly seen under natural resting conditions.

The circulation in individual capillaries of this area is frequently intermittent.

Intermissions in flow may occur alternately in two capillaries arising from the same arteriole.

When the flow ceases in a capillary, even during venous congestion, the vessel may become almost completely empty of corpuscles.

These observations indicate that individual capillaries are endowed with an occlusive mechanism which they may exert to prevent the passage of blood through their lumina.

Similar capillary behavior has also been observed in other skin areas.

AUTHOR.

Burwell, C. Sidney: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy. Am. J. M. Sc. **195**: 1, 1938.

The demonstrated phenomena of the circulation in pregnant women plus the evidence offered by the structure of the placenta lead to the following conclusions:

The changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) obstruction to venous return by the enlarged uterus, and (2) an arteriovenous leak through the placenta.

AUTHOR.

Snellen, H. A., and Nauta, J. H.: Roentgen Diagnosis of Coronary Calcification. Fortschr. a. d. Geb. d. Röntgenstrahlen. **56**: 277, 1937.

The authors point out the ease of diagnosing calcification of the coronary arteries by x-ray. This diagnosis was reported forty times in a year with calcification of the aorta or mitral rings showing simultaneously in six cases. In five instances there was necropsy confirmation of the roentgen-ray diagnosis. The diagnosis is made by dancing shadows in the location where arteries run, the patient holding his breath in deep inspiration. Kymography was found to be of great assistance.

KATZ.

DeTakata, Géza: Sympathectomy for Peripheral Vascular Disease. Arch. Int. Med. **60**: 990, 1937.

One hundred and twenty-six sympathectomies were performed on fifty patients. Twenty-four of these patients, with forty-six sympathectomies, have been followed for one to seven years. There were 16 operations in Raynaud's disease, 22 in Buerger's disease, 3 in poliomyelitis, and 5 in reflex dystrophy. Thirty were considered successful, 9 as improved, 6 as failures, and 1 patient died of coronary occlusion. Recently preganglionic section, as advocated by Smithwick, Freeman, and White and Telford, was used in operations for the upper extremities. Those patients who were found to have vessel spasm, as shown by heat tests or by vasodilator drugs, responded in most instances in a satisfactory way. Mistaken diagnosis, mistaken indications, improper stages of vascular disease, faulty technique, improper after-treatment, and poor follow-up are important factors in obtaining poor results. The surgeon who performs sympathectomies must be thoroughly familiar with peripheral vascular disease and its remissions and exacerbations and should use, either alone or in collaboration with physicians well versed in peripheral vascular disease, all the medicinal aids and physical therapy available at present.

MONTGOMERY.

Armstrong, Harry G.: The Blood Pressure and Pulse Rate as an Index of Emotional Stability. Am. J. M. Sc. **195**: 211, 1938.

A review of 700 examinations of candidates for flying training for the United States Army Air Corps shows that there are correlations of 0.98 for the stable group and 0.88 for the unstable group and a general correlation of 0.92 between the relative emotional stability of the individuals and their cardiovascular findings.

This correlation was obtained by adopting an arbitrary blood pressure level of 134/90 (+ or -3) and a pulse rate of 90 (+ or -3) and assuming that any reading above that level demonstrated a relative emotional instability.

The failures of previous workers to demonstrate a high degree of correlation between emotional stimuli and cardiovascular reactions and certain other inconclusive evidence and disagreements in the literature are explained by an analysis of the reaction patterns of the author's cases into five distinct groups, wherein it was shown that among the unstable candidates 21 per cent showed no abnormal blood pressure pattern and 66 per cent showed no abnormal pulse pattern. These dissimilar reaction patterns show the fallacy of mass statistics in such studies and demonstrate the necessity of studying the cardiovascular system as a whole in each individual in psychosomatic investigations.

The limitations and shortcomings of the described test for emotional stability are pointed out, as well as a suggestion for further studies which are necessary before the test is applicable to any situation other than the one from which the test was derived.

AUTHOR.

O'Neil, E. Everett: Suction-Pressure Therapy in Peripheral Vascular Disease. New England J. Med. **217**: 828, 1937.

Eighty cases of occlusion of the peripheral arteries treated by alternating suction and pressure have been reviewed. The best results were obtained in acute occlusion, when treatment was instituted before tissue changes had progressed too far. The poorest results were observed in arteriosclerosis of the extremities where diabetes was a complicating factor, and particularly where calcification of the arteries was shown by x-ray, denoting a low collateral potential. Negative-positive pressure treatment is of definite value in the early and moderately advanced cases of peripheral arteriosclerosis and thromboangiitis obliterans, exerting a marked beneficial influence on intermittent claudication and ischemic pain in these cases. Its value in the later stages is doubtful. In all types of chronic peripheral obliterative diseases to which suction-pressure therapy may be applied, it must be stressed that long periods of treatment are necessary for success. Since the tendency of any occlusive disease is to progress, it is important to keep ahead of it by frequent and continued applications of treatment.

MONTGOMERY.

Collens, W. S., and Wilensky, M. D.: Intermittent Venous Occlusion in Treatment of Peripheral Vascular Disease: An Experience With 124 Cases. J. A. M. A. **109**: 2125, 1937.

Compression of the proximal portion of the extremity up to 80 mm. of mercury for alternating periods of two minutes with two minutes of release applied continuously for as much as twelve hours a day had a decided therapeutic effect in the treatment of diseases associated with pathologic arterial changes. Early reports of this method have already appeared. The authors feel that the method is capable of increasing vascular capacity, as is evidenced by the following phenomena: relief of rest pain, increased walking capacity, regeneration of tissues, improvement in the nutrition of nails, and the growth of hair over areas which had become denuded as the result of obliterative arterial disease. They were able to note in one case the development of granulation tissue to such a degree of exuberance that it necessitated the use of silver nitrate on three different occasions in order to prevent the development of keloid.

MONTGOMERY.

Erratum

In the article, "Electrocardiographic Changes Occurring With Alterations of Posture From Recumbent to Standing Positions," by Louis H. Sigler, M.D., which appeared in the February issue of the JOURNAL, in Table I, on page 150, the last figure in the last column should be 4.0 (%) instead of 0.4 (%), as it now stands.